Text Book of Pharmacology

by

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CONTENT

CHAPTER 1

ORGANS INNERVATED BY THE AUTONOMIC NERVOUS SYSTEM

Autonomic Nervous System

The vegetative or autonomic nervous system, consisting of a central and a peripheral part, has the task of regulating all visceral functions of the organism. The central components are contained in the spinal cord and the brain stem. A specific pharmacological influence on the central autonomic nervous system is currently possible only to a limited extent, whereas the efferent part of the peripheral autonomic system has gained considerable importance in experimental and therapeutic pharmacology. Anatomical, physiological, and pharmacological considerations allow a differentiation of the autonomic system into a sympathetic and a parasympathetic division (Fig. 1). A schematic diagram of the efferent sympathetic and the parasympathetic systems is shown in Fig. 2 in order to demonstrate the location of synapses, together with the corresponding transmitter substances, and those pharmacological agents that act at these sites.

The pharmacology of the peripheral autonomic nervous system includes not only the pharmacological influence of the nervous system as such, but also that of the organs innervated by this system. In the target organs (smooth muscle, glands) drugs can imitate the excitation or the impairment of the autonomic system.

Cholinergic and adrenergic nerves are differentiated on the basis of the neurotransmitter, acetylcholine or norepinephrine (noradrenaline), which is released at the nerve ending. The expression, cholinergic nerve, cannot be restricted to the autonomic nervous system since the voluntary nerves leading to the skeletal muscles are also of the cholinergic type, i.e., acetylcholine is the transmitter sub-

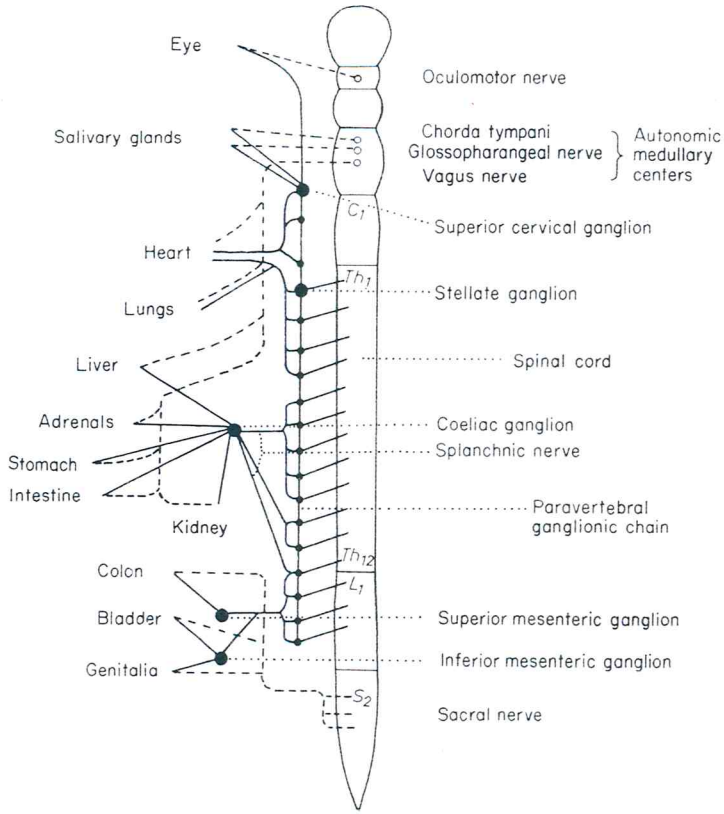


Fig. 1. A schematic representation of the peripheral autonomic nervous system. (—) Sympathetic; (- - -) parasympathetic.

stance at the motor end plate as well (cf. p. 119). The terms cholinergic and adrenergic may also be applied to the characterization of drugs. A cholinergic (cholinomimetic) compound mimics the action of acetylcholine released from the nerve ending, and an adrenergic compound similarly mimics the effect of norepinephrine. While the terms adrenergic drug and sympathomimetic drug are synonymous since the presence of adrenergic nerves is limited to the sympathetic system (at least in the peripheral part), the terms cholinergic drug and parasympathomimetic agent do not necessarily coincide. Thus, pilocarpine is a cholinergic compound as well as a parasympathomimetic agent, whereas succinylcholine is a cholinergic compound without being a parasympathomimetic drug since it acts only at the motor end plate.

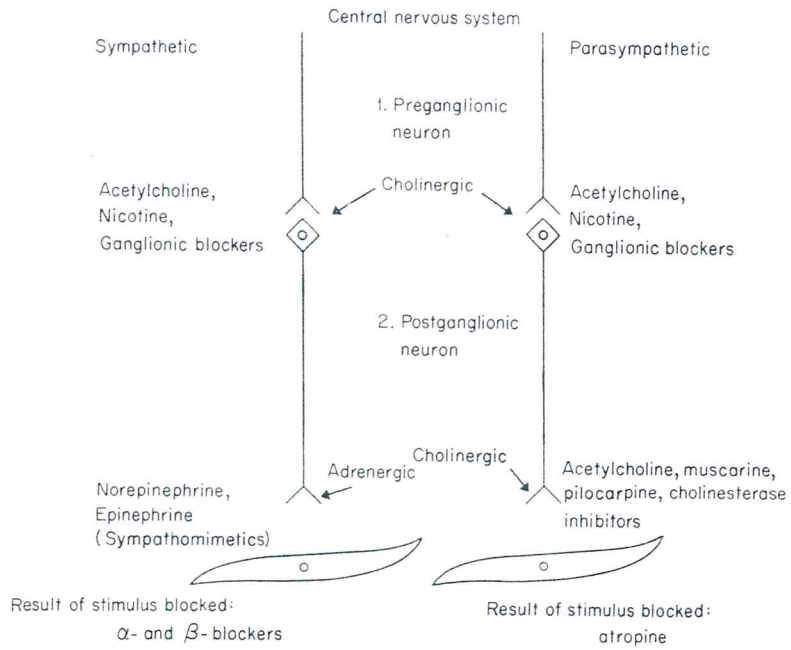


Fig. 2. A schematic representation of the peripheral efferent autonomic system showing synapses, transmitter substances, and excitatory or inhibitory drugs.

Autonomic drugs may be divided into two groups based on their principal mechanism of action.

1. Compounds that react directly with receptors for acetylcholine or norepinephrine (for the definition of "receptors" see page 313). Examples for such drugs in the parasympathetic system are nicotine, with a ganglionic site of action, in contrast to muscarine, pilocarpine, and atropine with a postganglionic site of action. Examples from the sympathetic system are nicotine, with a ganglionic site of action, and isoproterenol, dihydroergotamine, and dichloroisoproterenol showing a postganglionic site of action. Common to all these drugs is their reaction with the receptors themselves. Then either the adrenergic or cholinergic response occurs (direct-acting sympathomimetics or parasympathomimetics), or the receptors are occupied without subsequent reaction. In the latter case the action of the endogeneous transmitter substance is blocked (sympatholytic and parasympatholytic agents).

2. Compounds that interfere in some way with the metabolism of the neurotransmitters, acetylcholine and norepinephrine (synthesis, storage in the tissues, release from nerve endings, and metabolic degradation). Examples of these indirectly acting drugs are ephedrine, which causes the release of norepinephrine;

reserpine, which prevents the storage of norepinephrine; and physostigmine, which prevents the degradation of acetylcholine by acetylcholinesterase. Again, stimulation or blockade of the corresponding part of the autonomic system may be mimicked by these indirectly acting compounds. Therefore, the site at which the transmitters exert their cholinergic or adrenergic functions is of pharmacological importance. Acetylcholine exerts its transmitter function: (1) at the endings of the postganglionic fibers of the parasympathetic system (and of the sympathetic nerves leading to the sweat glands); (2) at all ganglionic synapses in the autonomic system; (3) at certain synapses in the central nervous system; and (4) at the motor end plate of skeletal muscle (cf. motor end plate, p. 119). The transmitter function of norepinephrine is limited to the postganglionic nerve endings of the sympathetic system (except those innervating the sweat glands) and to the central nervous system. In addition, dopamine probably has a transmitter function in the central nervous system (cf. Parkinsonism, p. 129).

Neither the neurotransmitters themselves, nor the various autonomic drugs always exert the same quantitative effect at all cholinergic or adrenergic sites. The pharmacological action of such compounds depends mainly on whether transmission at a peripheral or ganglionic (or motor end plate) site is involved; cholinergic transmission, for example, is blocked by atropine at postganglionic sites, by ganglionic blocking agents in the ganglia, and by curare at the motor end plate. Even if only the responses of the reacting organ are considered, differences in the reactivity to the same agent are frequently very large. There are, for instance, adrenergic substances which are primarily bronchodilators (isoproterenol) and others which are mainly vasoconstrictors (e.g., Paredrinol) or central nervous system stimulants (e.g., amphetamine). In several, but not all cases, the reasons for these differences in activity are known. The differences may be based on a differential distribution of the corresponding drug within the organism or in varying affinities of the compounds involved to the receptors in question. Recently it has become possible to obtain antibodies against the sympathetic nervous system. If such antibodies are administered to newborn animals, such animals do not develop any sympathetic nervous system. Their behavior is quite normal, but their reaction to adrenergic drugs is abnormal.

Postganglionic Site of Action

Parasympathomimetics

Like all cholinergic nerves (see also "motor end plate," p. 119), the postganglionic parasympathetic neuron and the neuroeffector junction in the reacting organ possess a complete "acetylcholine system": (1) the synthesizing enzyme, choline-acetylase; (2) a storage mechanism into which the continuously synthesized acetylcholine is taken up to be released again, either spontaneously or in larger amounts as a result of nerve stimulation; (3) receptors in the effector organ that react with acetylcholine, leading to local alterations in the properties of the cell surface; and (4) the degradative enzyme, cholinesterase (cf. Fig. 10). Two types of esterases are

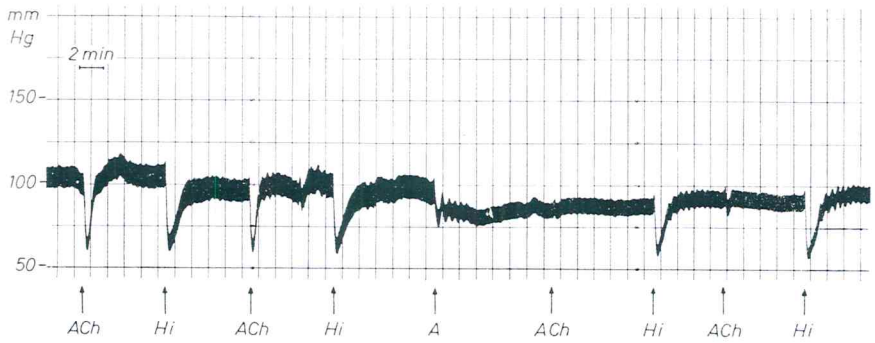


Fig. 3. The effect of atropine on the blood pressure responses to acetylcholine and histamine. The blood pressure of a cat was recorded by means of a pressure transducer on a recorder. The compounds were injected intravenously. ACh, 0.001 mg acetylcholine per kilogram, Hi, 0.004 mg histamine per kilogram; A, 2.0 mg atropine per kilogram. Atropine abolishes the effect of acetylcholine, while the action of histamine remains unchanged.

present in warm-blooded animals: (1) "true" cholinesterase (acetylcholinesterase), which is highly substrate-specific and always structurally bound, and (2) pseudocholinesterase, which belongs to the class of nonspecific esterases, and exhibits optimal activity at high substrate concentrations. This enzyme exists in solution in the body fluids. Along with the cholinergic receptors themselves, acetylcholinesterase is of particular pharmacological and toxicological interest within the "acetylcholine system" because specific inhibitors of this enzyme have become known.

When acetylcholine is injected or infused intravenously into experimental animals or man, the most marked symptoms arise from stimulation of postganglionic parasympathetic structures. These symptoms including lowering of blood pressure by vasodilatation (Fig. 3), negative chronotropic effect, negative inotropic effect on the atrium (Fig. 4), bronchial constriction, increase of intestinal tonus (Fig. 5), and increase of glandular secretion. The same symptoms may be observed in

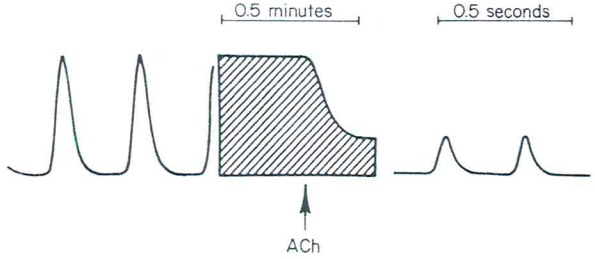


Fig. 4. The effect of acetylcholine on the contractile amplitude of the isolated guinea pig atrium. Isometric recording by means of a strain gauge connected to the recorder. Stimulation frequency, 4 Hz. The contractile amplitude decreases after the addition of 3×10^{-8} gm/ml acetylcholine. Note the two different recorder speeds.

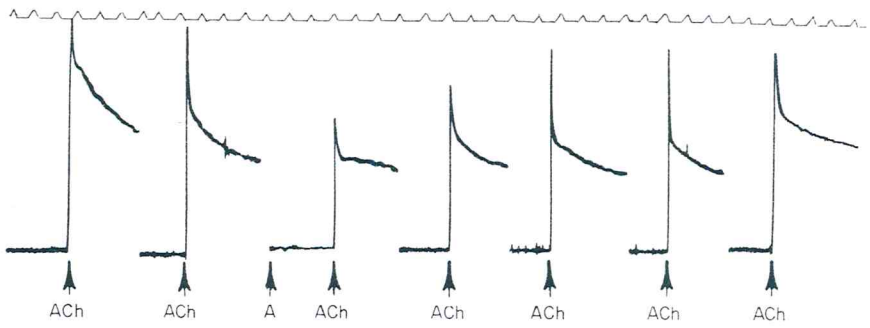


Fig. 5. The effect of atropine on the response to acetylcholine of the isolated guinea pig ileum. ACh, acetylcholine 5×10^{-7} gm/ml; A, atropine 10^{-7} gm/ml; time in minutes. The response to acetylcholine is reduced by atropine at this concentration; the effect of atropine can be slowly washed out.

poisoning with cholinesterase inhibitors (cf. pp. 13 and 263). Ganglionic structures and the motor end plate are less sensitive, so that their stimulation is masked by the above-mentioned parasympathetic effects. The duration of action of acetylcholine is very short since the compound is degraded with extraordinary rapidity (Fig. 3).

The mechanism of action of acetylcholine has excited the interest of physiologists and pharmacologists for a long time. A large number of investigations which in part have been conducted with the most modern and complicated methods have led to the following formulation of this mechanism: When acetylcholine is bound

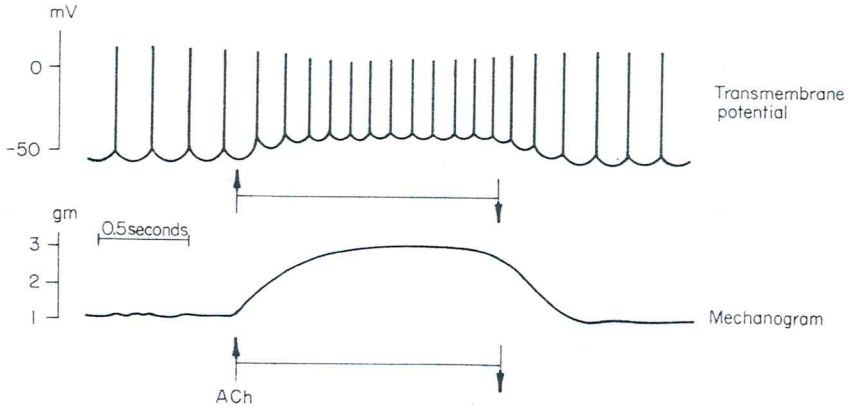


Fig. 6. The effect of acetylcholine on the transmembrane potential and the development of mechanical tension in smooth muscle (schematic). Acetylcholine diminishes the membrane potential and increases the frequency of the action potential; simultaneously muscle tension increases.

to the corresponding receptor in the cell membrane, the membrane permeability at this site is altered. The membrane instantaneously becomes more permeable towards potassium, sodium, and calcium ions, i.e., the preexistent flux equilibrium is disturbed and the membrane potential is altered. The direction of the change depends on the magnitude of the membrane potential and on the ratio between the increases in sodium and potassium conductance. In general, the actual membrane potential (E_m) may be expressed satisfactorily by the equation

$$E_m \sim \frac{[K]_i \times P_K + [Na]_i \times P_{Na} + [Cl]_e \times P_{Cl}}{[K]_e \times P_K + [Na]_e \times P_{Na} + [Cl]_i \times P_{Cl}}$$

where [K], [Na], and [Cl] represent the intracellular (subscript i) and extracellular (subscript e) concentrations of the respective ions. P is a measure of the specific membrane permeability for the designated ion. In the resting state the ratio $P_K:P_{Na}$ is approximately 1:0.01 which means that the potassium gradient (K_i/K_e) is by and large the determining factor. At the peak of excitation the relationship $P_K:P_{Na}$ reverses and E_m then becomes positive because the Na gradient is reversed. Under the influence of acetylcholine the membrane permeabilities for K and Na increase unequally such that the ratio of $P_K:P_{Na}$ may either

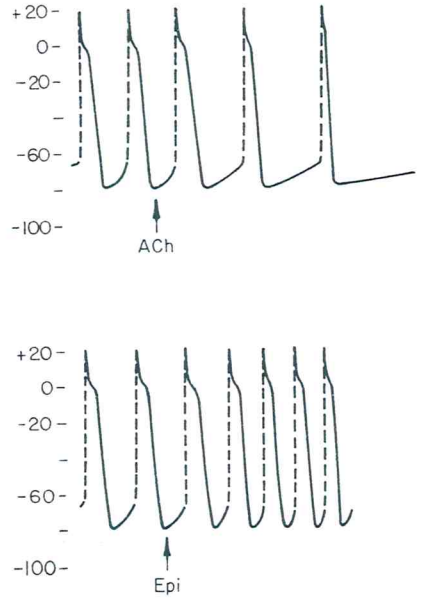


Fig. 7. Schematic representation of the effect of acetylcholine and epinephrine on the pacemaker potentials of the heart. Acetylcholine (ACh) prolongs diastolic depolarization and thereby diminishes the frequency of beating (negative chronotropic effect); epinephrine accelerates diastolic depolarization and thereby increases the frequency of beating (positive chronotropic effect).

increase (i.e., hyperpolarization) or decrease (i.e., depolarization). The final result can thus be either depolarization or hyperpolarization of the membrane. The former is the case at the motor end plate (cf. p. 119) in ganglion cells and in many smooth muscles, where depolarization leads to an increased action-potential frequency and thus to increased tonus (Fig. 6). On the other hand, at the pacemaker cells of the heart the comparatively larger increase in permeability to potassium causes a flattening of the diastolic depolarization, leading to a decrease of the pacemaker frequency or even to complete arrest (Fig. 7).

Through alterations in permeability the shape of the action potential in various organs may also be altered considerably. Figure 8 illustrates the deformation of the excitation process in atrial tissue. The extreme shortening of the duration of the action potential is presumably the reason for the inhibition of cardiac contractile force by acetylcholine (negative inotropic effect); the duration of the excitation is insufficient for a complete activation of the contractile system. In other cells the increased permeability mediated by acetylcholine leads to an inward flux of calcium which in turn activates the specific cellular function. Such a process has been demonstrated for glandular cells (e.g., secretion of saliva) and for cells of the adrenal medulla (secretion of epinephrine). In summary, it may be stated that the widely varying actions of acetylcholine are the result of one basic process—an increase in the ion permeability of the cell membrane when acetylcholine combines with the receptor located in the cell membrane.

Acetylcholine contains three spatially separated centers which are of importance for its biological activity: the positively charged nitrogen, the carboxyl oxygen

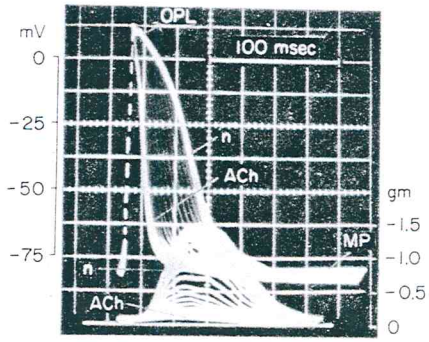
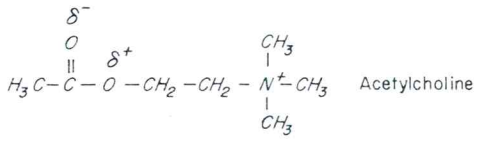
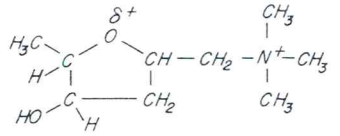


Fig. 8. The effect of acetylcholine on the shape of the action potential and contractile amplitude in the isolated guinea pig atrium. The action potential, obtained with intracellular microelectrodes, and the contractile force were continuously recorded and superimposed one upon the other. Top: Action potential with calibration on the left margin. Bottom: Contractions with the calibration on the right margin. Control values prior to the addition of acetylcholine are indicated by small letter *n*; addition of acetylcholine (5×10^{-8} gm/ml) changes the shape of the action potential and the contractile amplitude to the final values indicated by ACh. Note: The action potential becomes markedly narrowed (accelerated repolarization), the membrane potential (MP) becomes slightly more negative, the overshoot potential (OP) remains unchanged. Rapid depolarization (----) has been retouched.

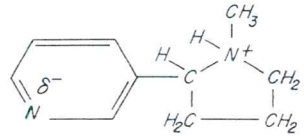
carrying a relative negative charge (δ^-), and the relatively electron-poor esteratic oxygen (δ^+). These conditions are illustrated in the corresponding formulas. (For details on tertiary and quaternary amines see p. 327.) Although the acetylcholine molecule possesses three reactive sites, only two of these at a time are necessary for the various actions of the compound since in all cases the acetylcholine receptors react with the quaternary nitrogen, an additional reaction only occurs with either the "positive" oxygen or the "negative" oxygen. The combination of the quaternary nitrogen and "positive" oxygen separated by a given distance is present in muscarine in a manner similar to that found in acetylcholine; another corresponding combination is found in nicotine.



Acetylcholine



Muscarine



Nicotine
1-Methyl-2-(3-pyridyl) pyrrolidine
or
3-[N-Methyl pyrrolidyl-(2')]-pyridine

According to our present conceptions, the interaction of a suitable drug with the postganglionic acetylcholine receptor occurs in a more complicated manner than previously assumed. The receptor possesses two "active centers"—(1) the anionic center and (2) the esteratic center. Both centers possess a negative charge (Fig. 9). All active parasympathomimetics possess methyl groups attached to the nitrogen atom (which functions as a cation) which contribute to the affinity at the anionic center as the result of van der Waals forces. A similar situation holds true for the esteratic center. At least two carbon atoms must be attached to the δ^+ charged oxygen in order that a compound possess agonist activity. This can be convincingly demonstrated, for example, with the muscarine molecule. Muscarine is a very potent agonist but the loss of the ring methyl group results in loss of activity. If the esteratic side chain is too long, branched, or aromatic, then the interaction can no longer take place; the compound has lost its intrinsic activity, but now acts as an inhibitor since it blocks the receptor by binding at the anionic center. The association of a drug with the anionic center probably determines its affinity and the reaction with the esteratic center its intrinsic activity (cf. p. 314).

There are two ways in which the action of acetylcholine can be mimicked: (1)

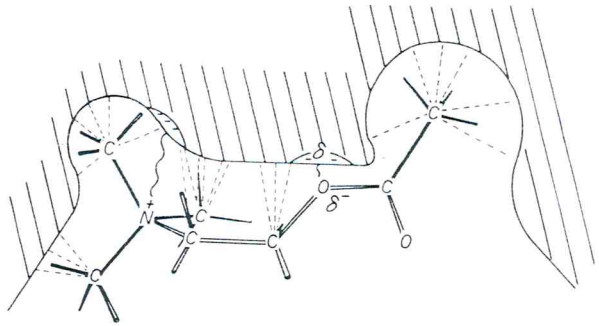


Fig. 9. Schematic representation of the binding of a molecule of acetylcholine to the postganglionic acetylcholine receptor. Along with the electrostatic binding (wavy line), Van der Waals forces (---- dashed lines) are involved at the anionic site (left) as well as the esteratic site (right).

with compounds that have the same site of action as acetylcholine (direct parasympathomimetics). Only those substances that are degraded less efficiently or not at all by cholinesterase are of practical use; and (2) compounds that inhibit the degradation of endogenous acetylcholine by cholinesterase (indirect parasympathomimetics or anticholinesterases).

Direct Parasympathomimetics

ACETYLCHOLINE. Acetylcholine is a strongly polar substance that contains a positively charged nitrogen and an electronegative oxygen atom. Both reactive sites of the acetylcholine molecule are necessary for the reaction with the receptor and with cholinesterase (Fig. 10); the chemical formulas indicate the active centers of both acetylcholine and of the direct parasympathomimetic agents. In spite of the large chemical differences among acetylcholine, pilocarpine, arecoline, and muscarine, the similarities and the distances between the active sites of the various molecules are obvious. It is also understandable that compounds which are not esters cannot be degraded by the esterase and thus have a longer duration of action.

CARBACHOL. Carbamylcholine chloride is degraded only slowly or not at all by cholinesterase. The subcutaneous injection of 0.25 mg causes marked parasympathetic effects such as increased secretion of sweat, saliva, and gastric juice, increased tone of the intestine and bladder, stimulated peristalsis, bradycardia, impaired heart contractions, and dilation of the arterioles and cutaneous vessels. In spite of this, the blood pressure does not always decrease because of opposing regulatory mechanisms. Introduction of a 1% solution into the eye causes a constriction of the pupil and, in glaucoma, a lowering of the intraocular pressure.

PILOCARPINE. Pilocarpine is an alkaloid from the leaves (folia jaborandi) of *Pilocarpus pennatifolius* that specifically stimulates the postganglionic para-

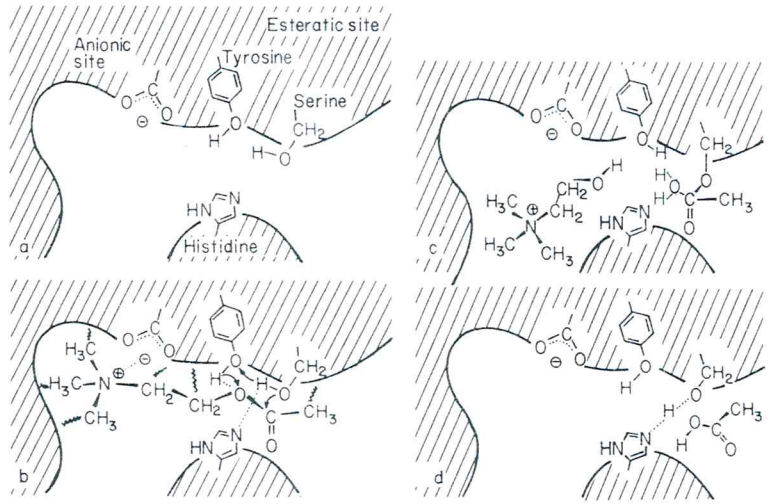
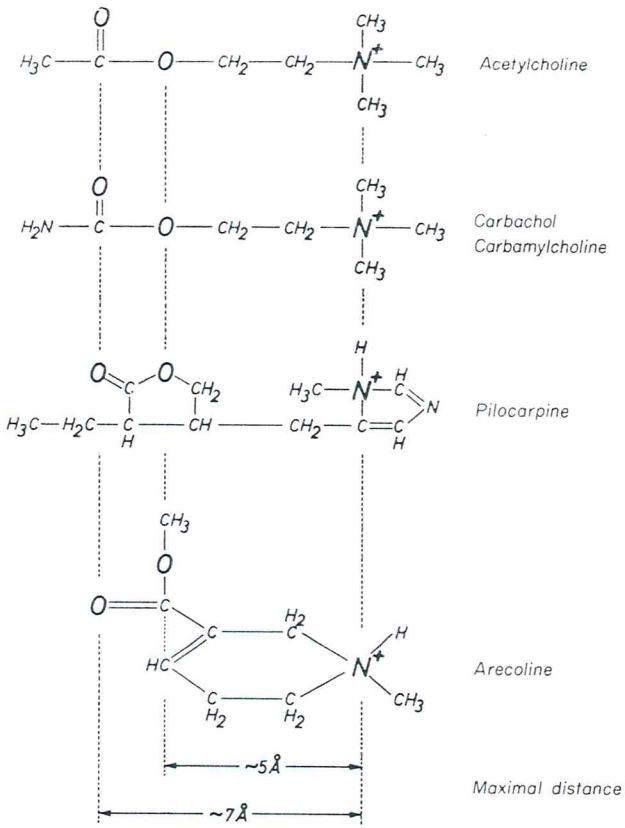


Fig. 10. Schematic representation of the reaction between acetylcholinesterase and its substrate acetylcholine. (a) Active site of the esterase with anionic and esteratic sites. For the anionic center it is probable that carboxyl or phosphate moieties are the functional chemical groups; for the esteratic center the hydroxyl groups of serine and tyrosine residues and also an imidazole nitrogen (histidine) are probably involved. The attachment of acetylcholine (b) provokes a shift of electrons and concomitantly a sequence of reactions that causes the hydrolytic cleavage of the ester group in acetylcholine. As a result of these conversions the esteratic center is intermediately acetylated (c). Choline dissociates more rapidly from its binding site than the acetyl moiety, so that deacetylation becomes the rate-limiting step. *Symbols:* WWW, Nonpolar binding forces (van der Waals' forces); ⌒, conversion reactions; and ····, electrostatic attraction, hydrogen bonding or resonance of the carboxyl group.

sympathetic receptors for acetylcholine. In general it acts like carbachol but its influence on the heart is more pronounced. This fact contraindicates its general use; only topical application to the eye can be recommended.

Therapeutic Use. Carbachol is often effective in the reversal of intestinal or bladder atonia caused by ganglionic blocking agents or occurring postoperatively. It also has been used successfully in cases of paroxysmal supraventricular tachycardia. Pilocarpine, like carbachol, is effective in glaucoma when applied locally to the eye. Lowering of the pressure is caused by enlargement of Schlemm's canal and Fontana's spaces in the iridial angle as the result of the drug-induced miosis.

Administration. Carbachol is usually given subcutaneously (not intravenously) in doses of 0.25 mg; the same dose can be repeated after 30–60 min if needed. Only with paroxysmal tachycardia refractory to other therapy can a dose of 0.05–0.1 mg be given very slowly by the intravenous route. To lower the intraocular pressure in glaucoma, a 1% solution of carbachol is dropped into the eye; pilocarpine hydrochloride is usually used as a 2% solution. In particular cases carbachol also may be given orally in doses of 1–4 mg several times daily.



Toxicity. The danger of a too potent depressant effect on the heart must always be kept in mind. Apart from the disturbance of cardiac function, sweating, diarrhea, nausea, vomiting, and spasms of accommodation may result. All such side effects, but also the desired effects, are abolished by the intravenous injection of atropine in doses of 0.5–1.0 mg or more.

Contraindications. With myocardial insufficiency there is a danger of cardiac failure; in bronchial asthma an attack may be provoked; and in hyperthyroidism, the danger of the occurrence of ventricular or supraventricular fibrillation exists. The use of pilocarpine as a sudorific is too dangerous.

MUSCARINE. Muscarine is isolated from the mushroom fly agaric (*Amanita muscaria*). It is not important in therapy but is of interest in experimental pharmacology. Muscarine acts, like pilocarpine, only on the postganglionic parasympathetic receptors and has no effect on the cholinergic ganglia and the motor end plate. To characterize the various effects of acetylcholine, this mode of action

is called muscarinic, while the action of acetylcholine on ganglia and end plates is called nicotinic because of the ability of nicotine to cause the same effect as acetylcholine at these sites. The varying sites of action may also be differentiated by three different types of anticholinergic agents: muscarinic actions are blocked by atropine; nicotinic actions on the ganglion by ganglionic blocking agents; and nicotinic actions at the end plate by *d*-tubocurarine.

ARECOLINE. Arecoline, an alkaloid from the betel nut, the seed of *Areca catechu*, possesses both muscarinic and nicotinic activity. In contrast to the quaternary parasympathomimetics, the tertiary substance, arecoline, penetrates well into the central nervous system (cf. p. 327). Its pK_a is about 7.8 so that *in vivo* a fraction of the total drug is always in the form of the free base. The activity profile for arecoline therefore always contains central nervous system components.

Indirect Parasympathomimetics (Anticholinesterases)

Cholinesterase inhibitors diminish the rate of acetylcholine degradation because they block the esterase more or less completely, depending on their concentration. Since acetylcholine is released continuously from the nerve endings of the autonomic system (thus maintaining parasympathetic tone), the concentration near the nerve endings depends on the amount of acetylcholine liberated and the amount degraded by the esterase per unit of time. This equilibrium is upset by anticholinesterases; the actual concentration of acetylcholine increases and parasympathetic tone increases. The same mechanism holds true at other cholinergic synapses (e.g., the motor end plate).

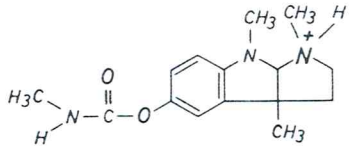
Cholinesterase inhibitors may be divided into two different chemical groups. One group consists of the quaternary ammonium compounds, which are related to acetylcholine. This group includes the alkaloid physostigmine (eserine), and the synthetic compounds neostigmine and pyridostigmine. The similarity of the active centers to those of acetylcholine explains how these compounds can react with acetylcholinesterase. The initial attachment occurs between the cationic nitrogen and the anionic center; subsequently carbamylation of the esteratic center occurs. Accordingly, the enzyme is blocked, since the decarbamylation proceeds more slowly than the deacetylation that is required for the splitting of ACh. Neostigmine not only has a high degree of affinity for the esterase but also, to a lesser extent, to acetylcholine receptors. A direct acetylcholinelike action of neostigmine can be demonstrated under certain experimental conditions. The second group includes the polyalkyl phosphates, which have a very high affinity to the esteratic site of cholinesterase. They have no therapeutic use but are widely used insecticides (cf. p. 263) and are of toxicological interest.

PHYSOSTIGMINE. Physostigmine, also called eserine, is an alkaloid from the seed of *Physostigma venenosum*. A dose of 0.5–1.0 mg of physostigmine salicylate causes the same symptoms as an infusion of acetylcholine or an injection of pilocarpine. Since intestinal stimulation and cardiac depression are rather marked, physostigmine should not be used therapeutically, especially since neostigmine and pyridostigmine are available and better tolerated.

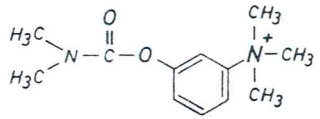
On the other hand, it is useful for local application to the eye in glaucoma, as a solution of 0.25–0.5%.

NEOSTIGMINE. A large number of physostigmine analogs have been prepared and tested. Among these are compounds such as neostigmine and pyridostigmine, which are preferable to the alkaloid in general therapy; the ratio between the desired actions (intestinal or motor end plate stimulation) and the side effects (cardiac depression) is more favorable with the synthetic compounds than with the natural product. Neostigmine methylsulfate (0.5–1.0 mg intramuscularly) or neostigmine bromide (7.5–30.0 mg orally) is given for bladder or intestinal atonia. In myasthenia gravis, oral administration must be individually determined; concomitant parasympathetic stimulation is undesirable and can be suppressed by atropine. The side effects correspond to those of pilocarpine and the therapy for an intoxication is similar.

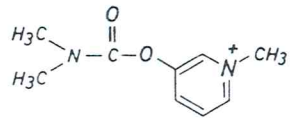
Pyridostigmine acts essentially in the same way as neostigmine, but the effects are slower in onset and are longer lasting. A compound acting similarly is edrophonium [ethyl-(3-hydroxyphenyl)-dimethylammonium chloride].



Physostigmine (Eserine)



Neostigmine



Pyridostigmine

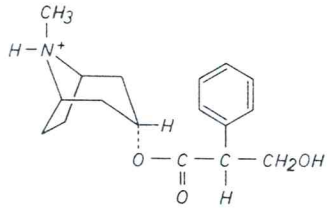
Cholinesterase inhibitors

Parasympatholytic Agents

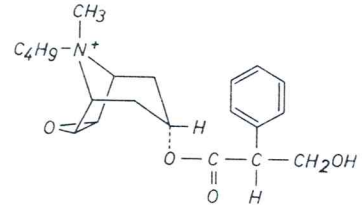
Cholinergic transmission can be blocked by various compounds, depending on the anatomic site at which it takes place: (1) in ganglia by ganglionic blocking agents, (2) at the motor end plates by drugs of the curare type, and (3) at the peripheral parasympathetic nerve endings by the atropine group (parasympatholytics) discussed below.

ATROPINE. Atropine is an alkaloid isolated from many species of Solanaceae, especially from *Atropa belladonna* (deadly nightshade), *Hyoscyamus niger* (henbane), and *Datura stramonium* (thorn apple). The native alkaloid is *l*-hyoscyamine, which racemizes to (±)-hyoscyamine (atropine) during isolation. These plants also contain, in varying quantity, scopolamine (hyoscine), which is chemically related to atropine and in some respects exhibits similar actions. Atropine is an ester of tropine and tropic acid.

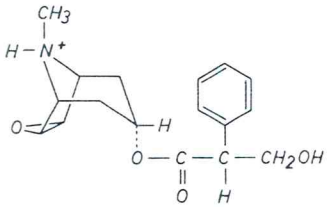
Atropine inhibits the action of injected acetylcholine or that liberated from the nerve endings by competition at the receptors of the target organ (Figs. 3 and 5). Like acetylcholine, it possesses a high affinity for the receptor, without the ability to stimulate it. Accordingly, it shows no activity in this sense (intrinsic activity, cf. p. 314). In the same way the action of other parasympathomimetics on these target organs, e.g., smooth muscle, glands, and heart, is diminished or abolished by atropine. The liberation of acetylcholine is not influenced. Cholinergic transmission in ganglia and at motor end plates is not inhibited by the usual doses of atropine but may be depressed by toxic concentrations.



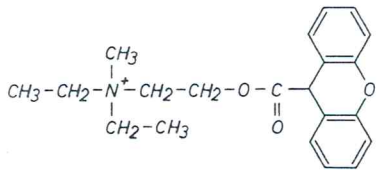
Atropine
Tropine ester of tropic acid



N-Butylscopolamine



Scopolamine (hyoscine)
Scopine ester of tropic acid



Methantheline

All the muscarinic effects of acetylcholine are suppressed by atropine. The extent of this inhibition, however, is not identical in all organs.

In the glands, inhibition of perspiration and salivation are the usual effects first observed. Also, the secretion of mucus in the nose, throat, and bronchi is reduced. The secretion of gastric juice is diminished only after high doses (at least 1 mg) and the acid concentration may even be increased. Pancreatic secretions may be decreased.

Eye accommodation is lost after large doses owing to paralysis of the ciliary muscle. The pupil diameter is increased due to a concomitant or somewhat later

occurring paralysis of the pupillary sphincter. This produces photophobia and in glaucoma patients (not in others), leads to a dangerous increase in the intraocular pressure because the drainage of the aqueous humor through Schlemm's canal is diminished. These phenomena may be observed after oral administration but are most pronounced upon local application of 0.5–1.0 mg into the conjuctival sac. Accommodation is disturbed for several days, and the pupil may be dilated for a week.

Inhibition of the cardiac branch of the vagus nerve (by doses of 1–2 mg intravenously or subcutaneously) leads to an increase of the pulse frequency to approximately 150/min. Formerly, it was postulated that atropine dilates the coronary vessels. In cases of coronary arteriosclerosis such a dilatation would not even be useful therapeutically, since the tachycardia would impose too great a load on the heart. It is not certain whether the dilatation of cutaneous vessels observed after large doses is caused by a slight ganglionic blocking action or by an action on the central nervous system.

The tone of the gastrointestinal tract and of the bile ducts is diminished earlier than the motility, especially in spastic conditions. The tone of the musculature of the urinary bladder falls. Actions on the ureter are only slight. Spasms in bronchial muscles, if they are caused by a cholinergic mechanism, may be abolished by atropine. This is only in part the case in bronchial asthma, and therefore the action of atropine in this disease remains unpredictable. Actions on the central nervous system are discussed in the sections on anti-Parkinson drugs and atropine poisoning. The antiemetic action of atropine, which is central in origin, is surpassed by that of scopolamine (cf., p. 167).

Oral doses of atropine are well absorbed. However, poisoning may also occur by absorption from the conjunctival sac via tear ducts and the mucous membrane of the nasal cavity. The greatest part of the alkaloid is degraded in the body, primarily in the liver; a small part is excreted in the urine. While atropine disappears quickly from the bloodstream, it remains bound for a long time at the site of action.

Therapeutic Use of Atropine. In order to relieve spasms in the region of the gastrointestinal tract, the bile duct, and urinary ducts, high doses of atropine with unpleasant side effects on salivation, the eyes, and cardiac frequency are always necessary. Atropine is usually not suitable for the treatment of gastric hyperacidity; methylatropine (see below) is preferred in the therapy of pylorospasm in newborns. Large doses of atropine (1–2 mg) effectively block the cardiac branch of the vagus in cases of cerebral pressure, electroshock, barbiturate anesthesia during operations on the floor of the mouth, and other conditions under which carotid sinus or vagus nerves are stimulated. Medium doses (0.5–1 mg) are sufficient for the inhibition of secretion from glands in the mucous membranes. This is important in premedication for anesthesia (cf. p. 180). Furthermore, atropine is useful in interrupting profuse secretion during vasomotor rhinitis. The medium dose is also sufficient to suppress the side effects of morphine on the gastrointestinal tract and the vomiting center. High doses of atropine (0.08–0.4 mg/kg) are a necessary antidote in poisoning with cholinesterase inhibitors of the organophosphate type. In addition, it is used to diminish the autonomic side effects in the therapy of myasthenia gravis with indirect parasympathomimetics. In the eye, atropine, with its long-lasting effect, is preferred to the short-acting homatropine if mydriasis is desired in iritis, prolapse of the iris, etc.

Contraindications. Atropine and drugs with a similar action must not be given in cases of glaucoma, suspected glaucoma, or prostate hypertrophy. Doses that increase cardiac frequency may be dangerous in coronary arteriosclerosis.

Atropine Poisoning. After ingestion of the fruit from the deadly nightshade or accidental oral consumption of eyedrops containing atropine, poisoning occurs which can have a highly dramatic course. Nevertheless, the prognosis is nearly always favorable since even a 100- to 200-fold increase in the therapeutic dose does not necessarily result in death. (Note the large therapeutic index.)

Characteristic symptoms are flushing of the skin, dryness of the mouth, disturbed accommodation, mydriasis, and tachycardia. Larger doses result in psychic alterations such as mental confusion, psychotic (especially manic) conditions and hallucinations. This state is sometimes followed by a long-lasting, deep coma. The body temperature may be increased as a result of diminished sweat secretion. This may lead to the mistaken diagnosis of such a poisoning as an infection. The blood pressure is usually changed very little. The patient's life is endangered by a central respiratory paralysis.

The therapy of poisoning consists of measures to decrease the body temperature, artificial respiration for respiratory disturbances, and intravenous injections of hexobarbital when excitation exists, but only in the lowest possible doses. Treatment with carbachol or neostigmine decreases the subjective complaints of the patients.

SCOPOLAMINE (HYOSCINE). Scopolamine is isolated from various species of Solanaceae, some of which contain atropine as well. As an ester of scopine and tropic acid, chemically it is closely related to atropine. As with atropine, only the levorotatory form of scopolamine is biologically active. Qualitatively, the actions of atropine and scopolamine on the autonomically innervated organs are identical; quantitatively the differences may be rather large. While the effect on the eye and on salivation is even more pronounced than after identical doses of atropine, cardiac frequency is influenced only slightly by scopolamine, as are the functions of the abdominal organs. In contrast to atropine, the effects on the central nervous system are primarily of a depressant nature (cf. pp. 130, 166, 167).

Poisoning by Scopolamine. Here as well the depressant actions on the central nervous system predominate, in contrast to atropine poisoning. After large doses a deep coma results. The effects on the eye are similar to those observed with atropine. The skin is also dry, but usually more cyanotic than flushed, since the respiratory center is inhibited.

HOMATROPINE. The long-lasting action of atropine on the pupil and accommodation necessitated the preparation of compounds with a shorter duration of action for dilation of the pupil during opthalmological examination. Homatropine is frequently used for this purpose. As in the case of atropine, the compound is an ester of tropine; tropic acid, however, has been replaced by mandelic acid. Instillation of a 2% solution of homatropine hydrobromide into the eye results in dilation

of the pupil for only 12–24 hr, and accommodation is less affected than upon instillation of atropine.

Spasmolytics with Atropinelike Action. In order to allow a better control of spasms in organs containing smooth muscle, efforts have been made for a long time to eliminate the many parasympatholytic side effects resulting from treatment by synthesizing compounds with a stronger affinity to the gastrointestinal tract, the bile duct, and the urinary ducts. The results have not been satisfactory, since again side effects on other organs cannot be avoided if spasmolytically active doses are used. Substances of this group are parasympatholytics with their principal effects on the gastrointestinal tract and decreased affinity for the glands, the heart, and the central nervous system; however, they do possess some ganglionic blocking activity which might be predicted from their chemical structure.

Methylatropine. This agent has largely displaced atropine in the successful treatment of pylorospasms in the newborn as a result of its very low central activity. The dosage for an infant is in the range of 0.1 mg (1–4 drops of a 0.1–0.4% alcohol solution). Body temperature must be monitored to avoid poisoning or to recognize it early.

Methantheline, methscopolamine, and *n*-butylscopolamine are all quaternary ammonium compounds and as such have some ganglionic blocking activity combined with an atropinelike effect, especially on the vagus nerve. Therefore, atropinelike side reactions always must be expected with pharmacologically active doses. Their absorption is poor and unreliable. Contraindications are the same as for atropine.

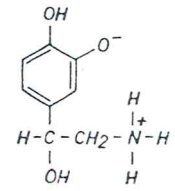
Adrenergic Compounds, Sympathomimetics

Adrenergic compounds have actions similar to those of epinephrine liberated from the adrenal medulla or to those of norepinephrine liberated from the sympathetic nerve endings, or, under certain circumstances, also from the adrenal medulla.

Epinephrine (Adrenaline) and Norepinephrine (Noradrenaline)

Both these compounds, called catecholamines, have essentially the same actions although there are some differences. The physiologically active, naturally occurring forms are the (−)-isomers, while the (+)-isomers are practically inactive.

Catecholamines and related compounds possess chemical groups which at different pH values can change their electrical charge. Thus, at physiological pH norepinephrine exists in the following form



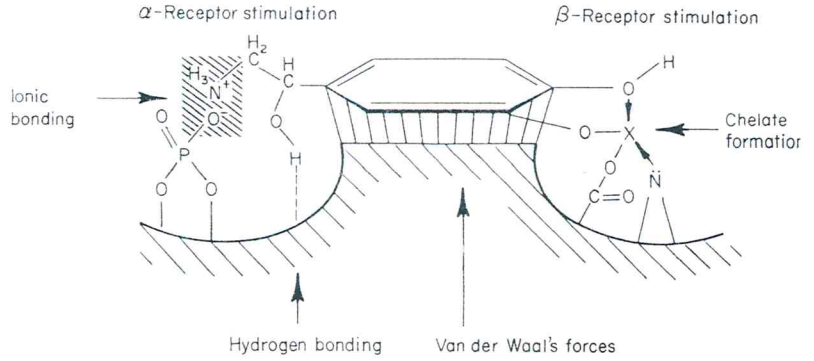


Fig. 11. Schematic representation of the hypothetical norepinephrine receptor and the binding of a norepinephrine molecule. ×, alkaline earth atom (Ca, Mg); —, main binding valences, →, secondary binding, ··, hydrogen bonds, ----, van der Waals forces.

The nitrogen atom accepts a proton and becomes positively charged, while the metahydroxyl group dissociates. These chemical characteristics enable norepinephrine, shown in the diagram, or related molecules to react with the corresponding tissue receptor, as shown in Fig. 11.

Action of Epinephrine on the Heart. Epinephrine increases the contractile amplitude, the shortening velocity, and the frequency of beating. Consequently, cardiac output increases. The influence is a direct one, since epinephrine acts in the same way on the isolated organ (Fig. 12). The rise in frequency is diminished but little by a reflex mechanism if the mean blood pressure is only slightly elevated; it is, however, moderated by means of the baroreceptors after a larger rise in blood pressure. For this reason, upon pretreatment with atropine (blocking of the cardiac vagus) the increase in frequency is correspondingly enhanced.

The influence of epinephrine on the nomotopic formation of stimuli in the sinus node is reflected by restoration of mechanical activity of a previously arrested heart and by an increased frequency of the beating heart.

While acetylcholine decreases the steepness of the diastolic depolarization curve, epinephrine shows exactly the opposite effect. The steepness of the depolarization curve increases and thereby the frequency of beating (Fig. 7). Moreover, after large doses to sensitive, especially damaged hearts, the formation of heterotopic stimuli is enhanced, producing extrasystoles. Under unfavorable conditions (oxygen deficit, hypercalcemia, hypokalemia, cyclopropane anesthesia), ventricular fibrillation may occur. Contributing heavily to this unfavorable development is the epinephrine-induced increase in O_2 consumption. After the high doses this higher oxygen consumption may lead to a lack of oxygen despite the dilation of coronary vessels caused by the drug. Thus, in cases of coronary arteriosclerosis, attacks of angina pectoris as well as ventricular fibrillation may be precipitated.

Vascular Actions of Epinephrine. The increase in the cardiac output after an intravenous dose of 0.02–0.03 mg of epinephrine raises the systolic, but usually not the diastolic, blood pressure in persons with normal circulation. Only high doses cause an increase of both parameters. This can be explained in the following way: Small, almost physiological doses constrict some vessels (skin and splanchnic

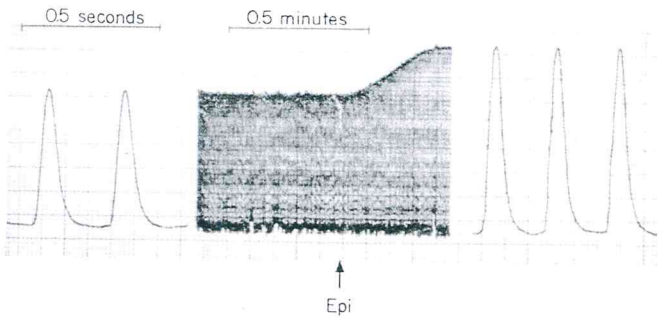


Fig. 12. The effect of epinephrine on contractile amplitude and frequency of the isolated guinea pig atrium. Isometric recording by means of a strain gauge connected to a recorder. Following the addition of epinephrine (2×10^{-8} gm/ml), contractile force and spontaneous frequency of beating increases. Note the two different recorder speeds.

region); other vessels, however, are dilated (heart and skeletal muscle). This action leads to a decrease (or lack of increase) in the peripheral resistance. Large doses of epinephrine as the result of the contraction of all vessels cause an increased peripheral resistance and thereby a higher diastolic pressure. Blood circulation through the kidney is decreased by epinephrine. Nevertheless, small doses do not decrease the glomerular filtration rate since the vasoconstriction occurs primarily within the vas efferens. Only after large doses is the quantity of filtrate diminished by a constriction of the vas afferens. Cerebral vessels remain largely unaffected by epinephrine, with the result that only as a result of increased systemic blood pressure is an accompanying passive increase in the cerebral circulation observed. The direct influence on the cutaneous capillaries is shown by extreme vasoconstriction near the injection site following intracutaneous injection of a few micrograms of epinephrine. In addition, capillary permeability is diminished. Solutions of corresponding dilution, when applied to mucous membranes, cause decongestion.

Actions on Other Smooth Muscles. Bronchial muscles are relaxed by epinephrine, especially when they are previously constricted. The relaxation of intestinal muscle and the pyloric antrum is only slight, as is the contractile activity on the sphincters of the cardia, pylorus, intestine, and bladder. Its effects on the uterus are irregular.

The pupils are dilated by contraction of the pupil dilator muscle. In practice, this happens only after large doses of epinephrine have been given intravenously or upon topical subconjunctival injection of the drug. In normal subjects dropwise application into the conjunctival sac does not cause mydriasis, but this may be achieved in especially sensitive patients, e.g., after blockade of the superior cervical ganglion and in patients with thyrotoxicosis or diabetes mellitus.

Action on the Central Nervous System. Since epinephrine does not penetrate the blood–brain barrier in significant quantities, it is not certain whether

after large doses, central symptoms such as anxiety and a feeling of weakness are based on a central action or whether they are only secondary to the peripheral cardiovascular effects. In any event, some compounds related to epinephrine, such as amphetamine, have marked central effects.

Metabolic Actions. Epinephrine increases the oxygen consumption of all tissues by a direct action on the cells. The basal metabolism is increased. With regard to these effects the following chemical steps have been elucidated. In many tissues epinephrine increases the transformation of adenosine 5′-triphosphate into adenosine-3′, 5′-phosphate, a cyclic nucleotide. Norepinephrine is less active and isoproterenol more active than epinephrine. (Concerning analogous actions of glucagon cf. p. 223). The cyclizing enzyme (adenyl cyclase) requires magnesium for its activity. The formation of active phosphorylase necessary for glycogenolysis is dependent on this cyclic adenosine monophosphate (Fig. 13). Analogous reactions are the basis of a lipolytic effect of epinephrine. In this case 3′, 5′-AMP activates a lipase. Through the cyclase-activating effect the blood level of glucose and free fatty acids rises. The cyclases are organ specific (isoenzymes), and can react differentially to drugs. It has been shown that cyclases and cyclic 3′, 5′-AMP are present in all cells. In numerous biological processes this cyclic nucleotide is involved as an intracellular "second messenger," thus mediating at the molecular level, the action of a drug or hormone. The acute effects of catecholamines on the heart and smooth muscle are not a primary result of the biochemical reactions just described but rather of membrane effects. Nevertheless, the increased glycogenolysis rapidly commences in the heart and contributes to the supply of energy.

Norepinephrine elicits responses generally similar to those observed after epinephrine. It increases the systolic pressure but, in contrast to epinephrine, it elevates the diastolic pressure even in small and moderate doses. This type of action on the blood pressure can be explained by a generalized vasoconstriction including the muscle vasculature and the resultant increase in peripheral resistance. Coronary vessels are not constricted. Cardiac frequency and cardiac output are not increased; indeed, they may be somewhat depressed. The frequency is not elevated because the baroreceptors are stimulated by the blood pressure rise with consequent feedback inhibition mediated by the vagus. Consequently, after pretreatment with atropine, norepinephrine increases cardiac frequency exactly as does epinephrine.

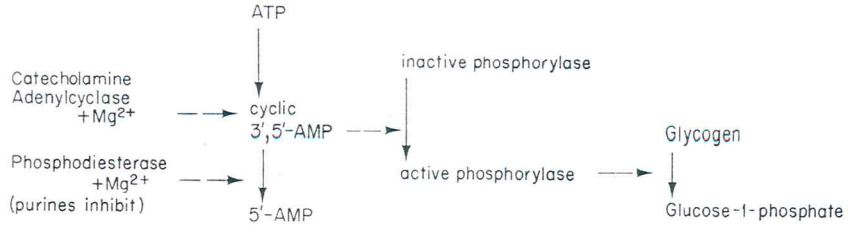


Fig. 13. The influence of catecholamines on carbohydrate metabolism.

Analogous to the action on the vessels of skeletal muscle, the relaxation of smooth muscle of the bronchi and the intestine is usually less after norepinephrine than after epinephrine. But also some muscle-contracting effects are quantitatively less than after epinephrine; examples are the cutaneous vessels, mucous membranes, kidney, and dilator pupillae. The blood vessels of the brain are constricted after norepinephrine, in contrast to epinephrine, so that despite the increase in blood pressure the cerebral circulation remains constant. The effects of norepinephrine on oxygen consumption and on the blood sugar are very moderate.

Distribution of the Catecholamines. Apart from the adrenal medulla, epinephrine is also found in the chromaffin cells distributed over various tissues. Norepinephrine can be extracted not only from sympathetic nerves and ganglia but also from the adrenal medulla and the autonomic centers of the brain stem, especially the hypothalamus. Differential centrifugation and electron microscopic investigations have shown that the catecholamines, bound to adenosine triphosphate, are contained in high concentration in cell granules and synaptosomes, which can be separated from nuclei, microsomes, and mitochondria. These granules have been found not only in the adrenal medulla but also in peripheral sympathetic nerve fibers and in the brain. The stored norepinephrine is presumably associated with sympathetic nerve endings, and epinephrine, with chromaffin cells. Dopamine is contained in the extrapyramidal areas of the brain. These storage forms have great pharmacological interest since several compounds are able to influence the storage. In dopaminergic neurons dopamine is not merely an intermediate, but possesses transmitter properties of its own (see e.g., page 129).

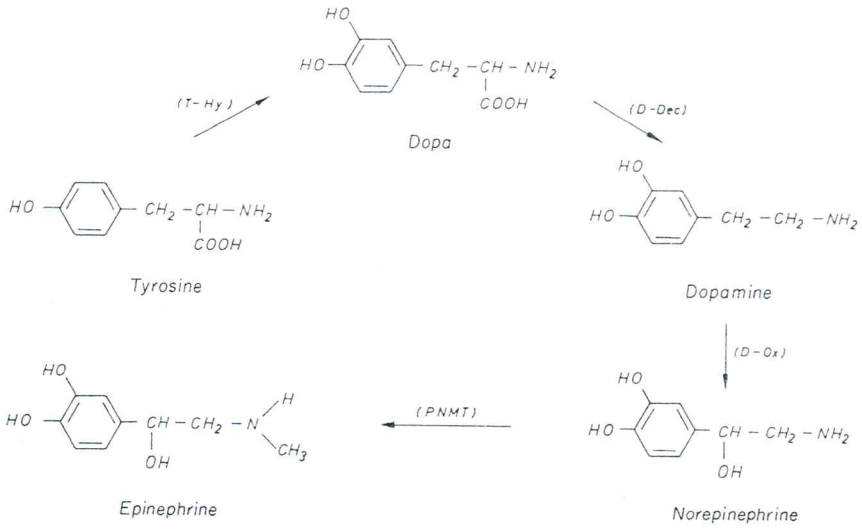


Fig. 14. The synthesis of norepinephrine and epinephrine. T-Hy, tyrosine hydroxylase; D-Dec, DOPA decarboxylase; D-Ox, dopamine-β-oxidase; PNMT, phenethylamine-*N*-methyltransferase, which is localized in the adrenal medulla.

Synthesis and Degradation of Catecholamines. L-Tyrosine is enzymically converted into (−)-norepinephrine [and in some cells into (−)-epinephrine], with L-dihydroxyphenylalanine (L-dopa) and dopamine as intermediates (Fig. 14).

The inactivation of released or injected epinephrine and norepinephrine (Fig. 15) occurs either by uptake into the tissue or by enzymic degradation. Quantitatively, the most important step in the enzymic degradation is dependent on the enzyme, catechol-*o*-methyltransferase, which methylates the hydroxyl group in the 3-position on the ring. Metanephrine and normetanephrine are thus formed. They are pharmacologically inactive and are deaminated by monoamine oxidase.

Only a small fraction is deaminated to 3,4-dihydroxymandelic acid prior to *o*-methylation (Fig. 15). Monamine oxidase does not play a decisive role in the initial degradation. (The central nervous system effects of monamine oxidase inhibitors are discussed in the section on psychotropic drugs.) Inhibitors of the *o*-methyltransferase (pyrogallol, pyrocatechol) show the expected effect. They increase the activity and prolong the effect of the catecholamines by slowing their degradation. This is analogous to inhibitors of cholinesterase. On the other hand, monamine oxidase is important for the degradation of intracellular catecholamines.

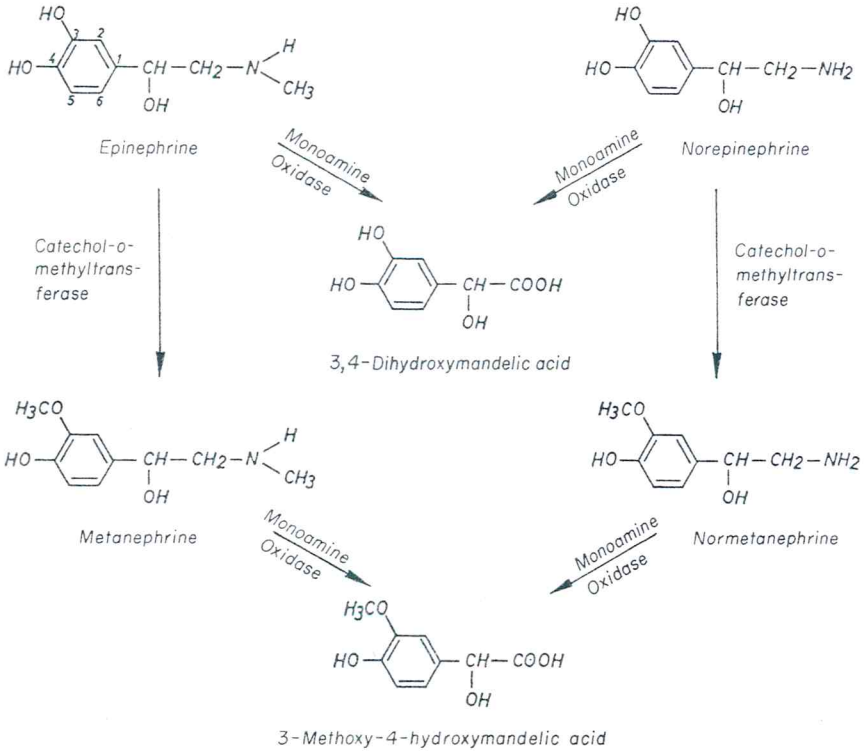
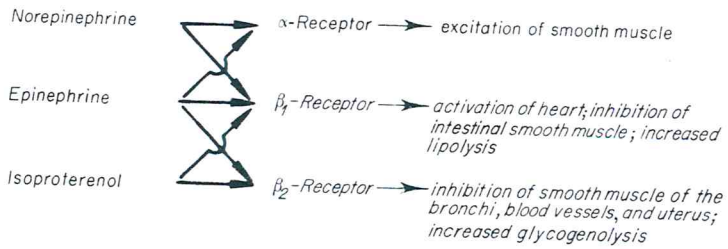


Fig. 15. Metabolic degradation of catecholamines.

The degradation of epinephrine to the red product, adrenochrome, which easily occurs in alkaline solution, does not play a role *in vivo* under normal circumstances.

α- AND β-RECEPTORS. Early investigators had already observed that the organ responses to sympathetic nerve stimulation and to epinephrine were not completely identical. Further differences became apparent with the attempt to abolish the stimulatory and inhibitory actions of epinephrine through the use of antagonists (sympatholytic agents). The classic representatives of this group (e.g., ergotamine) as well as more recently discovered drugs (e.g., phenotolamine) were found to block only the stimulatory effects on smooth muscle. On the other hand, inhibitory effects, for example, on the bronchial muscles as well as the general metabolic effects and cardiac stimulation were not prevented (see also adrenaline reversal, Fig. 17). These facts led to the postulation of two types of receptors for epinephrine—α-receptors that are blocked by drugs of the ergotamine type and β-receptors that are not blocked. The postulate was strengthened considerably by the discovery of a compound that selectively blocks the β-receptors. It is a derivative of isoproterenol, dichloroisoproterenol (cf. formula on p. 36), in which both hydroxyl groups on the ring have been replaced by chlorine. It was also apparent that isoproterenol itself reacts mainly with β-receptors. This results in the following scheme:



Epinephrine and norepinephrine have positive inotropic, chronotropic, and bathmotropic effects on the isolated heart, which can be inhibited only by β-blocking agents. The intestinal musculature does not fit simply into the above scheme, since the relaxation of the intestine following epinephrine is mediated by both α- and β-receptors and can be abolished only with a combination of both types of blocking agents. The catecholamine-induced contraction of the pyloric sphincter is prevented by α-receptor blockers.

SIDE EFFECTS AND TOXIC EFFECTS OF CATECHOLAMINES. Even relatively small doses—for instance, in local anesthesia—may lead in sensitive individuals to feelings of insecurity and anxiety, trembling, pallor, and cardiac palpitations soon after subcutaneous injection. These effects are especially frequent in hyperthyroidism. Larger doses, particularly after intravenous injection, result in a marked elevation in blood pressure, irregular heartbeat, and eventually cause death from ventricular fibrillation. The side effects and the toxic effects of epinephrine and norepinephrine do not differ significantly.

INDICATIONS AND USE OF CATECHOLAMINES. In practice it must be understood

that the stability of catecholamines in high dilution is rather poor. A very rapid decomposition occurs in alkaline medium. Some effects can be expected after oral doses only if these are about tenfold higher than those active parenterally, since the compounds are degraded quickly in liver and intestine. The extent of the effects after subcutaneous injection cannot be predicted with certainty, since the local vasoconstriction has an irregular influence on absorption and degradation.

Local Vascular Action. Application of dilute solutions (1:10,000 to 1:50,000) stops diffuse bleeding of tissue and mucous membranes. These compounds are used as additives to local anesthetics for subcutaneous injection because of their vasoconstrictor action since the marked diminution in tissue blood flow maintains the concentration of the local anesthetic for a longer time. The concentration of norepinephrine has to be double that of epinephrine. Resorptive poisoning is possible even with local applications (cf. also, p. 136).

General Vascular Effects. Along with replacement of blood volume, administration of norepinephrine is frequently lifesaving in cases of neurogenic shock. Since single or repeated injections of 0.5 mg norepinephrine increase blood pressure for only a few minutes each time, a prolonged infusion is indicated. The normal level of blood pressure should not be exceeded. This is especially the case for the therapy of shock in myocardial infarction. The dose must be adjusted to the resulting effect. Quantities of 0.01 (up to 0.02) mg of norepinephrine per minute are usually sufficient.

Epinephrine has been replaced by norepinephrine for such cases, since epinephrine results in undesirable side effects on the heart and general metabolism. However, epinephrine is preferred in anaphylactic shock, especially if asthmalike symptoms appear.

Cardiac Arrest. The potent action of epinephrine on nomotopic and heterotopic impulse formation is often successfully exploited, with cardiac arrest resulting from poisoning by local anesthetics, general anesthetics, quinidine, or in Stokes-Adams syndrome.

Intracardiac injection of 0.5 mg with simultaneous external heart massage is necessary if the drug no longer reaches the heart via the intravenous route. Norepinephrine is not indicated, but isoproterenol has been used very successfully.

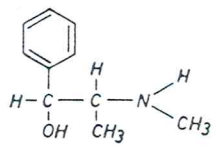
Bronchial Asthma. Epinephrine is useful in the treatment of asthma attacks. Subcutaneous injections of 0.25–0.5 mg (even up to 0.8 mg) are necessary; even better are the same doses by inhalation as an aerosol. Norepinephrine is not indicated; isoproterenol is preferred and its use is fully justified. However, if it is followed by epinephrine, dangerous cardiac complications may occur.

CONTRAINDICATIONS OF CATECHOLAMINES. Sudden cardiac arrest may occur after catecholamine administration in cases of coronary arteriosclerosis, hyperthyroidism, extreme hypertension, cerebral sclerosis, and related conditions. The tendency toward fibrillation is increased in the presence of cyclopropane, ethyl chloride, chloroform, or elevated calcium levels. The injection of local anesthetics containing epinephrine or norepinephrine can lead to gangrene in the fingers, toes, penis, nose, or ear. Local anesthesia in these areas must be induced without these additive agents.

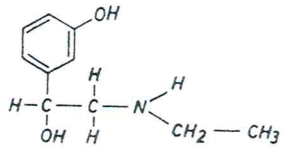
Sympathomimetics

In order to suppress certain actions of epinephrine and to enhance others, numerous phenylalkylamines have been prepared. It has become evident that partial or complete elimination of the phenolic hydroxyl groups in epinephrine results in compounds that are more stable, have a longer duration of action, and can be given orally. The loss of the side chain hydroxyl group and the introduction of an α-methyl group (propane derivative) accentuates the central effects (metamphetamine). The methyl group on the nitrogen is responsible for the actions on β-receptors, as demonstrated by the difference in the effects of epinephrine and norepinephrine. If the nitrogen side chain is extended, e.g., by replacement of the methyl group by an isopropyl residue, a pure β-receptor activator is the result.

Sympathomimetics with Vasoconstrictor Action. The oldest compound in this group is ephedrine, isolated from *Ephedra vulgaris*, a plant that has been used in China for several thousands of years. Oral doses of 25–50 mg of ephedrine hydrochloride elevate the blood pressure in mild cases of hypotension; the effect may last for hours. Fairly high parenteral doses may cause serious cardiac irregularities. Repeated injections of large doses result in an ever-diminishing effect, and finally none at all. This phenomenon is called tachyphylaxis, and it is also observed with other compounds related to epinephrine. The bronchodilator activity, the local vasoconstrictor activity for reducing swelling of the nasal mucous membranes, and also the weak central stimulant effect for the therapy of narcolepsy are rarely used now, since better drugs are available. Pholedrine has an action similar to that of ephedrine. Ethylphenylephrine has a beneficial and durable effect on blood pressure even on oral administration, which makes it useful in many cases of hypotension. Phenylephrine, a compound which almost exclusively stimulates α-receptors, and which lacks only the phenolic hydroxyl group in the 4-position to be epinephrine, has more long-lasting effects than the parent compound. It is used primarily as a local vasoconstrictor in conjunctivitis or in swelling of the nasal mucous membranes. Synephrine is an isomer of phenylephrine but the



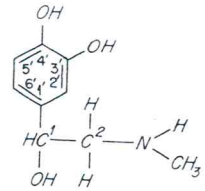
Ephedrine
1-Phenyl-2-methylamino-propanol



Ethylphenylephrine
α-[(Ethylamino)methyl]-m-hydroxybenzyl alcohol

single phenolic hydroxyl group is in the 4-position. Its activity is weaker, and no effect can be detected after oral administration of the usual therapeutic doses. The vasoconstrictor action of α-(aminomethyl)-m-hydroxybenzyl alcohol is evident only after parenteral administration. It may be used, therefore, in the same way as norepinephrine for the treatment of mild or moderate cases of neurogenic shock by prolonged infusion or through depot preparations.

TABLE I



Collection of Sympathomimetics[a]

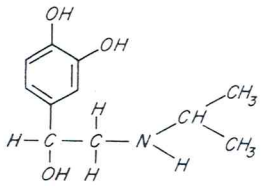
Generic name	Chemical designation	Primary activity[b]
Epinephrine	3,4-Dihydroxy-α[(methylamino)methyl]benzyl alcohol	
Norepinephrine	α-(Aminomethyl)-3,4-dihydroxybenzyl alcohol	
Nordefrin (α-methylnor-epinephrine)	α-(1-Aminoethyl)-3,4-dihydroxybenzyl alcohol	D
	α-(Aminomethyl)-*m*-hydroxybenzyl alcohol	V
Phenylephrine	*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol	V
Synephrine	*p*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol	V
Ethylphenylephrine	α-[(Ethylamino)methyl]-*m*-hydroxybenzyl alcohol	V
Pholedrine	*p*-[2-(Methylamino)propyl]phenol	V
Ephedrine	α-[1-(Methylamino)ethyl]benzyl alcohol	V, C
Amphetamine	α-Methylphenethylamine	C, (V)
d-Deoxyephedrine (Methamphet-amine)	*d*-*N*,α-Dimethylphenethylamine	C(V)
Isoproterenol (isoprenaline)	3,4-Dihydroxy-α-[(isopropylamino)methyl]benzyl alcohol	B
Metaproterenol (orciprenaline)	3,5-Dihydroxy-α-[(isopropylamino)methyl]benzyl alcohol	B
Bamethan	α-[(Butylamino)methyl]-*p*-hydroxybenzyl alcohol	D(U)
Nylidrin (buphenin)	*p*-Hydroxy-α-{1-[(1-methyl-3-phenylpropyl)-amino]ethyl}-benzyl alcohol	D(U)
Isoxsuprine	*p*-Hydroxy-α-{1-[(1-methyl-2-phenoxyethyl)-amino]ethyl}-benzyl alcohol	D(U)
Naphazoline	2-(1-Naphthylmethyl)imidazoline	L, V
Tetrahydrozoline	2-(1,2,3,4-Tetrahydro-1-naphthyl)-2-imidazoline	L, V
Xylometazoline	2-(4′-*tert*-Butyl-2′,6′-dimethyl-phenylmethyl)imidazoline	L, V

[a] The bold-faced groups in the epinephrine molecule can be omitted or replaced by others. The activity of epinephrine is then altered.

[b] The abbreviations signify V = primarily vasoconstricting, C = primarily central stimulant, B = primarily broncholytic, D = primarily vasodilating, U = uterine relaxation and L = local application only. The last three compounds are not readily derived from the epinephrine molecule.

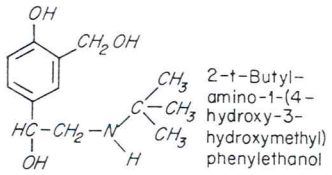
Sympathomimetics with Vasoconstrictor Action for Local Application. Chemically, most of the compounds mentioned below are only distantly related to epinephrine. For vasoconstrictor activity alone, a very simple molecule suffices as in the case of 2-aminoheptane [$CH_3(CH_2)_4CH(NH_2)CH_3$] which reduces swelling of mucous membranes. Substances in this group applied locally are used to decongest mucous membranes in rhinitis and in allergic and nonspecific conjunctivitis. Only a few of the numerous compounds in this class are mentioned here: naphazoline, tetrahydrozoline, and xylometazoline. These drugs, if given in excessive doses, may give rise to adrenergic side effects in sensitive patients (e.g., those suffering from hypertension or hyperthyroidism). Urinary retention and various circulatory disturbances have been observed. Infants are reported to have suffered from respiratory embarrassment as well as coma and shock. Xylometazoline is said not to induce these most serious side effects.

Compounds Related to Epinephrine with Bronchodilator Activity. Isoproterenol is the most important representative of this group. As described earlier, this compound has a pure β-receptor effect. Thus not only bronchial but also vascular muscles are relaxed. As a result of this vascular action the blood pressure should fall, but the vasodilation is compensated by the cardiac effects of isoproterenol and by reflex mechanisms. Apart from the desired bronchodilation, subjectively unpleasant side effects sometimes appear, such as palpitation and angina pectoris. On the other hand, the positive influence on the generation of nomotopic and heterotopic stimuli may be utilized in cases of cardiac arrest, Stokes-Adams syncope, etc. In cases of shock accompanied by vasoconstriction, isoproterenol can be used advantageously in connection with other measures.



3,4-Dihydroxy-α-[(isopropylamino)methyl]-benzyl alcohol

Isoproterenol, isoprenaline
isopropyl norepinephrine



2-t-Butyl-amino-1-(4-hydroxy-3-hydroxymethyl) phenylethanol

Salbutamol

Isoproterenol is best used for bronchial asthma as an aerosol of 1% solution. A quickly repeated inhalation may cause death as a result of a toxic effect on the heart. The propulsion gas used in commercial sprays may be involved in such incidents. Perlingual administration (single doses of 10–20 mg) is usually less effective. Oral doses or injections should be given only in very special circumstances. The isomer of isoproterenol, metaproterenol (orciprenaline) has a similar but longer-lasting action. Although the broncholytic action (β_2-receptors) is the same, the effect on the heart (β_1-receptors) is approximately 15–20 times less pronounced. For bronchodilation salbutamol seems to be particularly favorable, since this drug possesses only β_2-mimetic effects (i.e., little influence on heart and

circulation). In some cases the inhalation of epinephrine is more effective than that of isoproterenol, possibly because epinephrine causes shrinkage of the bronchial mucuous membranes as the result of vasoconstriction.

Other Sympathomimetics with Inhibitory Effects on Smooth Muscle. As was pointed out above, the affinity of an adrenergic drug to α- or β-receptors depends on the length of the substituent at the nitrogen atom. If the side chain is extended, adrenergic agents are obtained which result in β-receptor stimulation, i.e., vasodilator and tocolytic action while the other effects are suppressed. Examples are substitutions with the butyl radical (Bamethan), nylidrin, which contains a 1-methyl-3-phenylpropyl group and isoxsuprin with the phenoxypropyl moiety. The dilating activity primarily affects the vessels in skeletal muscle (resistance vessels) and less so those in the skin (capacitance vessels). Since the stroke volume and cardiac frequency are simultaneously increased, the blood pressure does not fall following moderate doses in normotensive individuals. The circulating blood volume and cardiac output are larger. The tachycardia is perceived unpleasantly as palpitations.

Therapy with bamethan and nylidrin may be attempted in the treatment of disturbances in peripheral circulation, such as intermittent claudication and Raynaud's gangrene. Dose levels have to be determined individually since the sensitivity toward "adrenergic" side reactions differs widely and the therapeutic index is rather small. These compounds are contraindicated in hyperthyroidism, hypertension, paroxysmal tachycardia, and angina pectoris. Drugs of this group like isoxsuprine and nylidrin have proved useful in preventing imminent abortion and in cases of premature labor. The β-receptor activation results in inhibition of the premature uterine activity.

Cocaine. Apart from its local anesthetic action (cf. p. 137), cocaine possesses adrenergic activity. This can be particularly well demonstrated in an experimental animal in which the effect of epinephrine or norepinephrine is potentiated after pretreatment with cocaine. Cocaine in the usual concentrations is not an inhibitor of *o*-methyltransferase or of monamine oxidase. A second effect of cocaine in the sympathetic system is the inhibition of the action of indirectly acting sympathomimetic agents (such as tyramine and ephedrine). The explanation for these paradoxical effects is to be found in the following mechanism of action. Epinephrine or norepinephrine may be removed from the extracellular space via three pathways: combination with the receptor, uptake into the cell (biological inactivation)

Injected or liberated NE → receptor, then degradation
→ uptake into the cell (granules)
→ enzymatic degradation in the extracellular space

and extracellular enzymic degradation. If any one of these processes is inhibited, the concentration of catecholamine available for the remaining mechanisms increases. One such example was presented earlier, namely, the inhibition of catechol orthomethyltransferase, by pyrogallol or pyrocatechol, producing an increase in the effect of epinephrine. Cocaine, on the other hand, has the property of affecting the membrane of cells that store catecholamines, rendering them impermeable to epinephrine and norepinephrine. Thereby, the amount that can be taken up into these cells is diminished and the concentration of catecholamines at the receptor site increases. But cocaine also inhibits the penetration of indirectly acting sympathomimetics, so that these are no longer capable of releasing norepinephrine and thus become inactive after cocaine treatment. Therefore both effects, the potentiation of catecholamine action and inhibition of the indirect-acting sympathomimetic action, are not contradictory but can be attributed to a common mechanism.

Mechanism of Action of Compounds Related to Epinephrine. The various actions of compounds related to epinephrine may be accounted for partly by their different affinity toward α- and β-receptors of the adrenergic system. In addition, there is some organ specificity. Some compounds in this series, such as tyramine, ephedrine, amphetamine, and methamphetamine, have no direct action on the receptors but probably exert their effect through liberation of norepinephrine from extragranular storage sites. Moreover, they impair the reuptake of norepinephrine into the cell. Both processes increase the norepinephrine concentration at the receptors. Repeated doses reduce the amount available from the storage sites; the effect, thus, decreases correspondingly. This is the explanation for the tachyphylaxis mentioned in the discussion on ephedrine. If catecholamines have been eliminated from the storage depots by pretreatment with reserpine, the indirect sympathomimetics are inactive; their pharmacological activity is restored after the administration of small doses of norepinephrine. Sympathomimetic agents may thus be divided into directly and indirectly acting ones, depending on whether they react with the receptor or whether they liberate endogenous norepinephrine, and accordingly raise the extracellular norepinephrine concentration.

Antisympathetic Agents

The tone of the sympathetic system can be decreased by pharmacological intervention at various points in the autonomic nervous system. The following possibilities exist.

1. Inhibition of autonomic centers in the central nervous system. Examples of this kind of action are those of reserpine discussed in detail on page 40 and clonidine (cf. p. 42). Apart from its central action, reserpine has a well-defined peripheral mode of action (see below).

2. Inhibition of ganglionic transmission in the sympathetic system; a whole series of compounds block ganglionic transmission (cf. ganglionic blockers, p. 38).

3. Decrease of the ability to store norepinephrine in postganglionic nerve endings

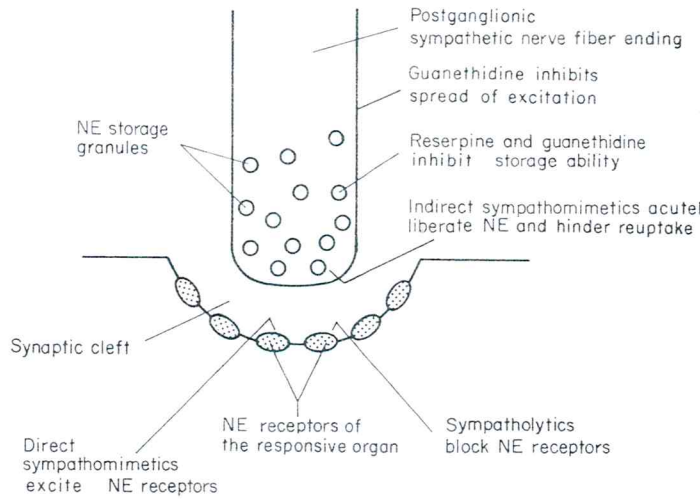


Fig. 16. A schematic representation of the postganglionic sympathetic nerve fiber and the effector tissue with an indication of some of the possibilities for affecting the system with pharmacological agents. See the text for details; NE, norepinephrine.

upon treatment with reserpine and guanethidine. The incoming stimulus is incapable of releasing norepinephrine from these depleted nerve endings; transmission is thus blocked.

4. Blockade of the receptor for norepinephrine by compounds with high affinity and low intrinsic activity—sympatholytics.

5. Synthesis of a "false norepinephrine" from a supply of unnatural precursors. This novel way of influencing the sympathetic system is possible with α-methyldopa (α-methyldihydroxyphenylalanine).

6. Inhibition of the biosynthesis of catecholamines by tyrosine hydroxylase inhibitors. This procedure has been attempted in the treatment of phaeochromocytoma.

7. "Chemical sympathectomy" can be performed by transient destruction of adrenergic nerve endings by the exogenous compound 6-hydroxydopamine.

Inhibition of the Storage Facility

The adrenergic transmitter substance is stored in the endings of sympathetic nerve fibers. The norepinephrine is bound to adenosine triphosphate in subcellular granular structures. Every incoming nerve impulse releases a corresponding amount of norepinephrine that then can react with the receptor in the target organ (see Fig. 16). A prerequisite for the smooth functioning of such a system is the presence of a sufficient amount of norepinephrine in the storage granules. If the ability for storage is diminished or abolished in the nerve ending, the effectiveness of sympathetic excitation is correspondingly reduced due to lack of transmitter and thereby the tone of the sympathetic nervous system is decreased.

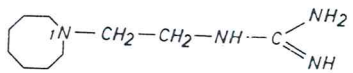
Norepinephrine is stored not only in the granules, since a smaller part of the neuronal norepinephrine is also found outside the granules (extragranular storage). The indirectly acting sympathomimetics principally release the norepinephrine stored extragranularly.

The alkaloid, reserpine (chemical structure, cf. p. 40) is the prototype of those compounds which inhibit storage in the sympathetic granules. Thus they are antisympathetic agents and are clinically useful. Drugs of this group deplete the norepinephrine content of peripheral tissues; reserpine has additional, specific central effects. These central actions may be caused by an analogous mechanism related to that found peripherally since the content of certain biogenic amines in the central nervous system, such as norepinephrine, dopamine, and serotonin, is reduced after reserpine.

If these "antistorage" substances are given parenterally in rather high doses, there is an initial sympathomimetic effect, similar to that resulting from an intravenous infusion of norepinephrine. It is caused by norepinephrine that is rapidly released from the granules. On the other hand, if treatment is started with low doses, insufficient quantities of norepinephrine are liberated per unit of time to produce such effects; this procedure should naturally be chosen for decreasing the tone of the sympathetic system. The main action of these drugs is a lowering of blood pressure, an effect seen especially in cases of hypertension (cf. therapy of hypertension, p. 56). Sympathetic vasoconstrictor reflexes are diminished. The rates at which norepinephrine is depleted from various tissues are different. The functions of the parasympathetic system are not impaired.

The side effects are based mainly on the decreased functioning of the sympathetic system: orthostatic complaints, nasal congestion, fatigue, asthenia, and sudden fainting due to the fall in blood pressure. The loss of sympathetic tone can result in bradycardia, vomiting, diarrhea, and loss of accommodation. Eventually decreased kidney function may cause retention of water and sodium. Saluretics balance the latter side effect. Treatment of long duration or high doses may cause anxiety reactions, depression, and extrapyramidal disturbances (probably a result of dopamine depletion). The action of a single dose of reserpine lasts much longer (2–3 days) than the presence of reserpine in the organism can be demonstrated. This phenomenon may be explained as follows: reserpine irreversibly damages the grana that will store norepinephrine. These vesiclelike structures originate by separation from the endoplasmic reticulum close to the nucleus. The newly formed grana must slowly pass along the entire axon in order to replace the damaged vesicles at the nerve endings.

Apart from its effect on amine storage, guanethidine also influences the membrane properties of the postganglionic nerve endings (local anesthetic action). Thus the release of norepinephrine upon stimulation as well as norepinephrine reuptake is inhibited. Since guanethidine penetrates but poorly into the brain, it does not produce sedation, in contrast to reserpine. Consequently, emotional



Guanethidine
[2-(Octahydro-1-azocinyl)-ethyl]-guanidine

disturbances may lead to a dangerous increase in blood pressure owing to epinephrine mobilized from the adrenal medulla in large quantities, and to the increased sensitivity of peripheral vessels to catecholamines. This supersensitivity of target organs can be observed in all cases in which norepinephrine release is prevented by surgical or pharmacological measures. Considerable variation in the required doses is observed for this drug from patient to patient. The side effects of guanethidine, like those of reserpine, are caused by the inhibition of the sympathetic system. Orthostatic complaints are likely and sometimes there is difficulty in ejaculation.

Chemical variation of the guanethidine structure has led to the synthesis of some analog compounds. Their inhibitory effects on the sympathetic system are only in part comparable to that of guanethidine (e.g., guanoxan, guanacline = cyclazenin) and they may exhibit unexpected side effects, e.g., hepatotoxicity after guanoxan or irreversible orthostasis after guanacline. Prenylamine, a diphenylpropylamphetamine, has a weak indirect sympathomimetic effect and interferes with the uptake of catecholamines into the heart and other tissues. In contrast to reserpine or guanethidine, it does not lower the blood pressure. It is used in the therapy of coronary artery disease, although it is not clear whether a relationship exists with its "antistorage" action.

Sympatholytics

Figure 17 shows the so-called epinephrine reversal as seen in the blood pressure of a cat. Whereas epinephrine, under normal conditions, results in a transient increase in blood pressure, it produces a fall in blood pressure when the animal has

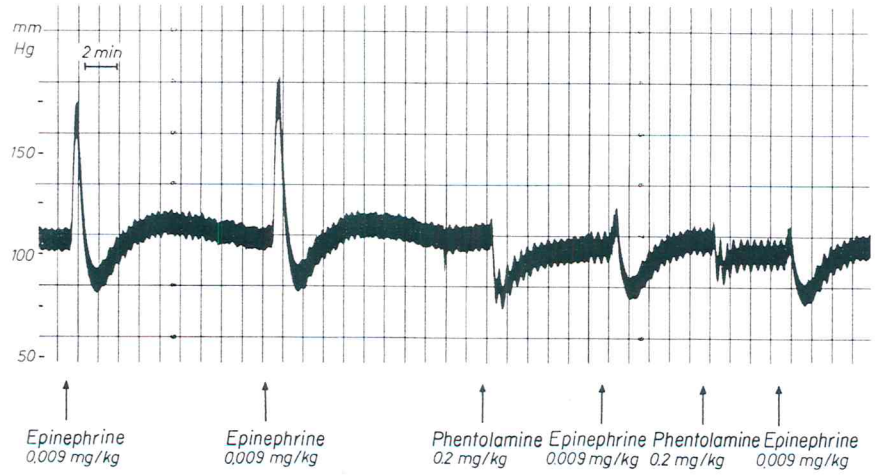


Fig. 17. The effect of phentolamine on the blood pressure responses to epinephrine. The blood pressure of the cat was recorded by means of a pressure transducer connected to a recorder. Epinephrine and phentolamine were injected intravenously. Epinephrine lowers the blood pressure after the administration of phentolamine (epinephrine reversal).

been pretreated with a sympatholytic agent (e.g., phentolamine). This effect is caused in the following way. Epinephrine reacts with both α- and β-receptors with a quantitative predominance of α-excitation (vasoconstriction) and the blood pressure increases as the sum of both processes. Phentolamine reacts with, and blocks, only α-receptors. Subsequently injected epinephrine now can combine only with β-receptors, leading to vasodilatation and decreased blood pressure.

The first sympatholytic compounds which were found to give such an epinephrine reversal were the alkaloids, ergotamine and yohimbine. The sympatholytic effect of yohimbine is rather weak and unsuited for therapeutic use. Ergotamine, an ergot alkaloid, also cannot be used for its sympatholytic properties because this activity is generally overshadowed by a direct stimulating effect on smooth muscle (cf. p. 45). Ergotamine has two opposing actions on the smooth muscle of blood vessels: direct vasoconstriction and vasodilatation via its sympatholytic properties. Partial hydrogenation of the native ergot alkaloids changes the ratio between these effects. The direct action on smooth muscle decreases in favor of the sympatholytic effect. Dihydroergotamine and the dihydro derivatives of the three ergotoxine alkaloids have found limited application as sympatholytics.

A whole series of synthetic compounds which belong to various chemical groups have sympatholytic activity (cf. Fig. 18). In this case one is dealing exclusively with a blockage of the α-receptors. Two compounds, namely phenoxybenzamine and phentolamine, have acquired a certain importance in therapy. The indications for the use of this particular group of drugs are limited. Hypertension is not significantly improved while on the other hand therapy of peripheral circulatory disorders is sometimes successful. The elevation of blood pressure, expected during surgical intervention or occurring spontaneously in phaeochromocytoma patients can be suppressed by phentolamine or phenoxybenzamine. The application of these drugs in the diagnosis of chromaffin tumors should be replaced by the determination of urinary catecholamines because of the danger of lethal shock. In addition to its antiadrenergic action, phentolamine has a direct vasodilator effect. Those side effects should be mentioned which are common to this group of drugs, i.e., excitatory effects upon the heart, expressed as tachycardia, arrhythmias, and angina pectoris, as well as disturbances of the intestinal tract (vomiting, abdominal pain, and diarrhea). These sympatholytics are, therefore, contraindicated in cases of coronary artery disease and ulcers. Tolazoline (2-benzyl-2-imidazoline) has in addition a weak histaminelike effect; this explains the stimulation of gastric secretion and the danger of the development of ulcers.

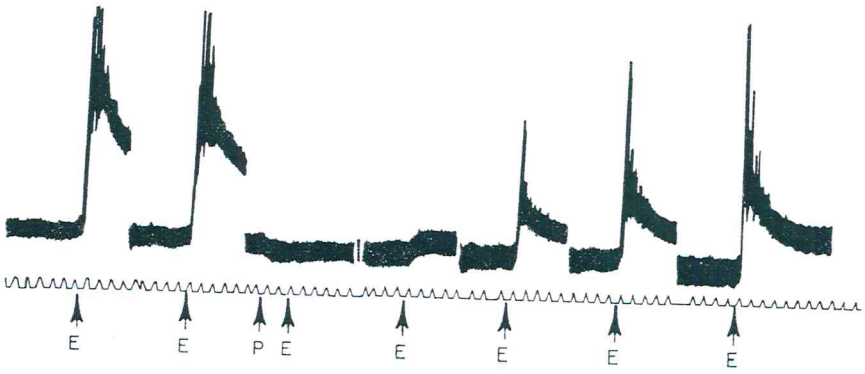


Fig. 18. The effect of phentolamine on the response to epinephrine of the isolated vas deferens of the guinea pig. E, epinephrine (adrenaline) 2×10^{-6} gm/ml; P, phentolamine 10^{-5} gm/ml; time in minutes. The excitatory effect of epinephrine is abolished in the presence of phentolamine; the sympatholytic agent can only be washed out slowly.

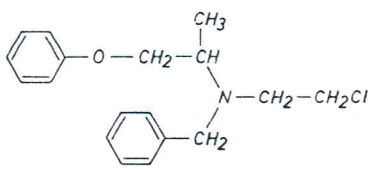
β-Receptor blocking drugs have won great importance in experimental medicine. The pharmacological actions and clinical applications of these drugs are determined by their affinity to either β_1 or β_2 receptors. Such was not the case for the initially discovered drugs of this class (dichloroisoproterenol and propranolol). On the other hand, the newer drugs of this class show a certain degree of organ specificity. Practolol is for instance a cardioselective β_1-blocker that does not induce bronchoconstriction as observed with the other drugs.

In general, all β-adrenergic blocking agents show a "quinidine"-like action on the heart (see p. 75). This "quinidine"-like action is not dependent on the optical isomerism of the compounds, whereas the β-adrenergic blocking activity is restricted to the levorotatory (—)form. For therapeutic application one should consider whether the β_1-activity or the "quinidine"-like action is desired. In almost all cases the "quinidine"-like action predominates in the dosage used clinically. This particularly holds true for the frequently successful treatment of angina pectoris, e.g., use of alprenolol (see p. 77). Clinical indications for blockade of β_1-receptors only are hyperexcitability of the heart, e.g., the hyperkinetic heart syndrome and juvenile hypertension, in which at least initially only cardiac output is increased. The difference between the dose that causes exclusively β-receptor blockade and the dose at which "quinidine"-like effects appear is unique to each drug. This difference is particularly pronounced for INPEA (1-*p*-nitrophenyl-2-isopropylaminoethanol) and practolol. One should always keep in mind that in some types of myocardial insufficiency small concentrations of endogenous catecholamines are required to maintain basal function. β-Blockers can be dangerous under these conditions.

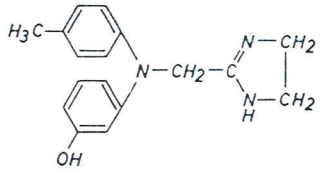
Synthesis of a False Transmitter Substance

The normal transmitter substance, norepinephrine, is formed from dihydroxyphenylalanine (dopa). Replacement of this naturally occurring precursor by α-methyldopa results, at least in part, in the formation of α-methyl dopamine and α-methyl norepinephrine instead of dopamine and norepinephrine (Fig. 19). Other unnatural precursors, for example, α-methyl-*m*-tyrosine, lead to the storage of "false" transmitters. α-Methyl norepinephrine is taken up and stored in the granules in the same manner as norepinephrine itself, and liberated again upon nerve stimulation. The important fact is that the α-methyl derivative has only a fraction of the adrenergic activity associated with norepinephrine in humans. Sympathetic tone is decreased probably in the main as a result of central effects.

α-Receptor blockers

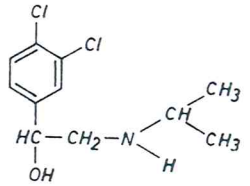


Phenoxybenzamine
N-(2-Chloroethyl)-N-(1-methyl-2-phenoxyethyl)-benzylamine

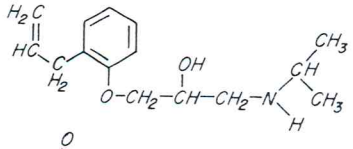


Phentolamine
2-[N-(m-Hydroxyphenyl)-p-toluidinomethyl] imidazoline

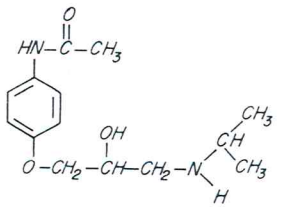
β-Receptor blockers



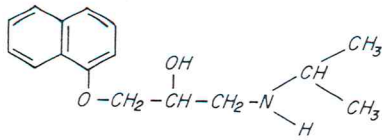
Dichlorisoproterenol
3,4-Dichloro-α-(isopropylaminomethyl)-benzylalcohol



Alprenolol
1-Isopropylamino-3-(2-hydroxy-o-allylphenoxy) propane



Practolol
4-(2-hydroxy-3-isopropylamino-propoxy)acetanilide



Propranolol
1-Isopropylamino-3-(1-naphthyloxy)-2-propanol

The possibility of autonomic regulation is retained since increased sympathetic nerve activity does lead to release of increased amounts of transmitter substances. Such treatment is preferable to ganglionic blockade or to complete depletion of the granular stores, both of which are associated with the danger of orthostatic collapse.

Apart from the mechanism of action just described, a second reaction has only limited importance for the pharmacological effect of α-methyldopa. It is a competitive inhibitor of the decarboxylation of dopa to dopamine and possibly of 5-hydroxytryptophan to 5-hydroxytryptamine (serotonin). As a result, the tissue

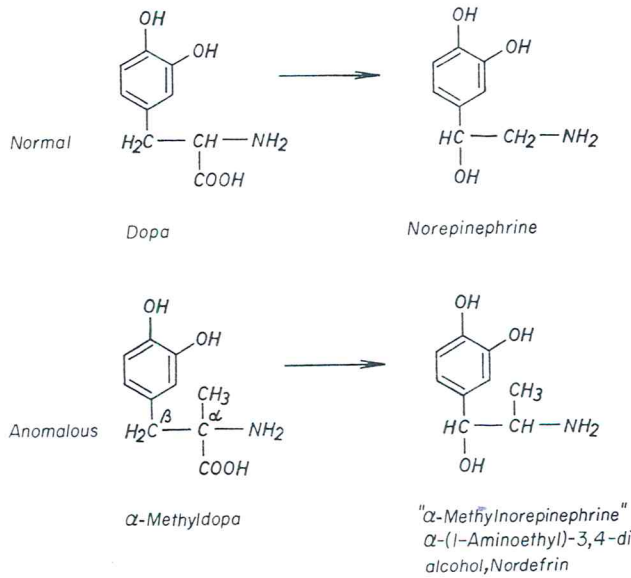


Fig. 19. Synthesis of a false transmitter.

levels of these amines fall only transiently. After administration of α-methyldopa (1.5–3.5 gm orally or 1.0–1.5 gm intravenously per day), the blood pressure decreases with 2 or 3 days, especially in hypertensive states, while blood pressure regulation is well maintained. α-Methyldopa, thus, seems to be a valuable addition to those drugs used for the treatment of hypertension (cf. p. 56).

Side effects during the first days of treatment include marked sedation, fluid retention, and disturbances caused by predominance of the parasympathetic system. In some cases therapy must be discontinued because of severe headaches, fever, or hemolytic anemia resulting from an autoimmune process. Isolated reports describe symptoms of psychosis (visual and acoustic hallucinations) as well as Parkinsonism after administration of large doses over long periods of time.

Ganglionic Site of Action

Ganglionic Blocking Agents

Substances that act specifically to prevent the transmission of stimuli at synapses of autonomic ganglia are called ganglionic blocking agents or ganglioplegics. Since transmission in all ganglia is a cholinergic process, the synapses of both the sympathetic and the parasympathetic system are always blocked simultaneously. Since sympathetic tone is normally predominant in vascular innervation—and parasympathetic tone in the innervation of the stomach, intestine, and gall bladder—treatment with ganglionic blocking agents may particularly affect these systems. Usually, however, in antihypertensive therapy only the decrease in vascular tone is desired and the blockade of the parasympathetic ganglia represents an undesired side effect (cf. hypertensive therapy, p. 56).

Acetylcholine is the transmitter in all ganglia of the autonomic system (see Fig. 2). In this sense, the catecholamine producing and storing cells of the adrenal medulla correspond to postganglionic sympathetic nerve fiber endings. Acetylcholine acts on the ganglionic synapses as it does at the motor end plate, depolarizing the membrane of the postganglionic nerve cell, triggering a stimulation of this second neuron. This nicotinelike action may be modulated by means of excitation or inhibition of muscarinic receptors and by adrenergic mechanisms in the ganglion itself. Administration of acetylcholine, even when it is protected from hydrolysis by a cholinesterase inhibitor, does not demonstrate the effects of ganglionic stimulation because the peripheral muscarinic effects of acetylcholine on the circulation (lowering of blood pressure) will mask the results of ganglionic stimulation signaled by a rise in blood pressure. Injected acetylcholine can only produce an increase in blood pressure after elimination of the muscarinic effects of acetylcholine by atropine. The effect is a result of stimulation of sympathetic ganglia and the similarly functioning adrenal medulla.

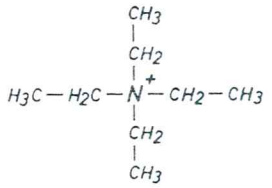
Nicotine

Nicotine (cf. formula, p. 9), an alkaloid obtained from tobacco leaves, in small doses results in acetylcholinelike stimulation of ganglia because of its depolarizing action; this relationship is illustrated on page 3. Since the adrenal medulla behaves much like a ganglionic structure, adrenal catecholamines are liberated by nicotine. Larger doses of nicotine, after initial stimulation quickly block ganglionic transmission owing to prolonged depolarization. This action corresponds to the depolarization at the motor end plate after decamethonium or succinylcholine. As nicotine is also capable of blocking ganglia when applied locally, such application was used earlier in analytical experiments on the physiology of the autonomic nervous system. The overall actions of nicotine, with their mixture of stimulatory and paralytic effects on sympathetic and parasympathetic ganglia, are so erratic and unfavorable that

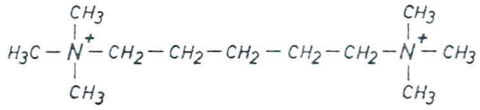
the substance is quite unsuited as a therapeutic drug (concerning nicotine and tobacco).

Ganglioplegics

The simplest compound which experimentally acts to stimulate ganglia and thus possesses the same type of action as nicotine is tetramethylammonium ion. If the methyl groups are replaced stepwise with ethyl groups, the ganglionic stimulating activity is gradually lost. Tetraethylammonium is a pure ganglioplegic—a membrane-stabilizing substance. Ganglionic blocking agents are related chemically and pharmacologically to the neuromuscular blocking agents of the curare group and the latter drugs in large doses have ganglioplegic activity. Compounds of both groups react with the acetylcholine receptor without then provoking depolarization (loss of intrinsic activity). The receptor, however, is blocked, and the transmitter substance is rendered inactive. All ganglionic blocking agents possess a "cationic head" of tetrasubstituted nitrogen. Secondary, tertiary, or quaternary amines



Tetraethylammonium



Pentamethonium (C-5)
Pentamethylenebis[trimethylammonium]

may be involved (cf. p. 327). If two "cationic heads" are present, a distance of 5–6 atoms between them is optimal.

Pharmacological Actions. The intravenous administration of a ganglionic blocking agent results in a fall of blood pressure in man and experimental animals due to the abolition of transmission in sympathetic ganglia responsible for vasomotor impulses. Often with small or moderate doses the blood pressure is only slightly reduced in the supine position. On getting up or on long standing the loss of vascular regulation may trigger orthostatic collapse.

The dilation of peripheral vascular areas does not necessarily lead to an increased blood flow and a consequent increased oxygen supply, since these parameters are dependent not only on the diameter of the vessels but also on the blood pressure. Since the blood pressure decreases after administration of ganglionic blocking agents, an increased blood flow cannot usually be expected. Under the influence of ganglionic blocking agents, the actions of catecholamines and acetylcholine on peripheral end organs are potentiated in a manner similar to that found if the corresponding ganglia have been removed by surgical means.

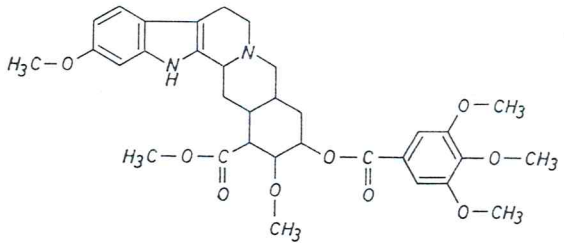
Apart from these actions on the sympathetic system, there appear analogous ganglionic blocking effects in the parasympathetic system. The smooth muscle tone of the gastrointestinal tract, the gall bladder, and the urinary tract is decreased. Atonic constipation is frequent and even paralytic ileus may be encountered. Correspondingly, difficulty in micturition has been observed, especially in cases of prostatic hypertrophy. Sexual impotence may occur. The eyes show mydriasis and failure of accommodation; salivary secretion is reduced. The concomitant inhibition of sweat glands, on the other hand, is based on the blockade of sympathetic ganglia.

Central Site of Action

Reserpine

Reserpine is the main alkaloid from the roots of the *Rauwolfia* species that occur in India and other tropical countries. *Rauwolfia serpentina* has been in use in Indian folk medicine for a long time. With regard to its chemical structure, it is of interest to mention that reserpine, in common with many other psychotropic agents, contains an indole moiety.

Reserpine



Reserpine has a sedative effect in man and experimental animals. Even after higher doses there is considerably less somnolence than after hypnotics with an equivalent sedative effect. In contrast to the hypnotics, there is little effect of reserpine on the electroencephalogram nor does it prevent convulsions induced by convulsant agents, and even in high doses it does not cause anesthesia. The aggressiveness of animals and mental patients is depressed.

Surgical lesions in various brain areas suggest that reserpine has a site of action in the brain stem, particularly the hypothalamic region. Such localization is probable since the stores of norepinephrine, dopamine, and 5-hydroxytryptamine (serotonin) normally found in the mesencephalon and hypothalamus are depleted following treatment with reserpine. Concomitant with this depletion, the tissue loses its ability to store the amines. It is not completely clear whether there is a relationship between the sedative effect and the lowered content of serotonin. A series of findings point in that direction. Thus, syrosingopine, a substance similar to reserpine, while possessing comparable sympatholytic activity, has milder sedative effects. With this compound the serotonin content of the brain is changed very little while the norepinephrine content falls. Peripheral sympathetic nerves lose their norepinephrine after pretreatment with reserpine (cf. p. 31).

Duration of Action

Reserpine is not detectable in the brain of rabbits about 2 hr after intravenous administration. The concentration of amines in the stores, however, remains depressed for several days before the initial value is reestablished. Thus, the changes in amine metabolism as well as the pharmacological effects following a single dose last much longer than the length of time that reserpine is detectable. It is currently not clear whether the origin of this phenomenon in the central nervous system is the same as in the peripheral sympathetic system (cf. p. 32). The maximal effect of this drug is achieved only after days or even weeks of daily oral administration. When the treatment is discontinued the effects subside slowly over days or weeks.

Side Effects

The loss of sympathetic tone results in a number of side effects: miosis, ptosis of the eyelids, sinus bradycardia with slowing of atrioventricular conduction, increased glandular secretion, nasal congestion, and diarrhea. Moreover, after larger doses there may be orthostatic complaints, aggravation of cardiac insufficiency, hypothermia, increase in body weight, and occasionally stomach ulcers due to increased acid production. Prolonged administration may lead to symptoms of Parkinsonism, such as a fixed facial expression, rigidity, or tremor. Myasthenia and myalgia, anxiety, nightmares, and serious depressions have been described. The therapeutic use of reserpine will be described in detail in the section on the therapy of hypertension (cf. p. 56); the drug is also used as a tranquilizer.

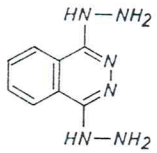
Appendix

Insufficient knowledge is available on the site of action of some drugs to organize them meaningfully into a system. The following section deals with compounds which influence the function of the autonomic nervous system and play a certain role in the therapy of hypertension and disorders of peripheral circulation.

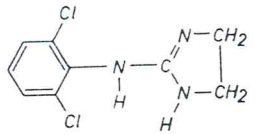
Hydralazines dilate blood vessels primarily by a direct action and possibly influence autonomic centers. The result is a fall in blood pressure. They also stimulate β-receptors to a slight extent and inhibit the vasoconstrictor effect of some drugs. Even if the blood pressure is reduced, renal blood flow is increased.

The side effects of hydralazines result partly from lowered blood pressure (headaches, vertigo, faintness, trembling, and paresthesia in the extremities) and partly from the relative dominance of the parasympathetic system (nausea, vomiting, diarrhea, intestinal spasms, stomach ulcer formation, etc.). Orthostatic collapse may be caused by depressed circulatory reflexes. Localized edema and allergic reactions have also been described. Prolonged administration of high (above 0.4 gm) daily doses may cause symptoms of rheumatoid arthritis. If medication with hydralazine is not discontinued, a picture of acute disseminated lupus erythematous develops in nearly 10% of all cases. This can be controlled by corticosteroids after the initiating drug has been discontinued. The paresthesia or peripheral

neuritis results from an antivitamin B_6 effect of hydralazine and may be improved by administration of vitamin B_6.



Dihydralazine
1,4-Dihydrozinopthalazine



Clonidine
2-(2,6-Dichlorophenylamino)-2-imidazoline

Hydralazines are useful in the treatment of hypertension and disturbances of peripheral circulation. A combination with other hypotensive agents is recommended because of the side effects. A commercial preparation is available which contains 10 mg of dihydralazine per 0.1 mg of reserpine.

Clonidine lowers the blood pressure. The mechanism of this response is not yet completely understood. Inhibition of central autonomic centers is probably the major determinant. This is supported by the frequent occurrence of sedation. Cardiac output and cutaneous blood flow are reduced; the compound stimulates α-receptors. After discontinuation of this drug the blood pressure may rise to values higher than those observed prior to clonidine administration. The urinary excretion of catecholamines is decreased. While this imidazoline derivative is used as an antihypertensive agent, ethyl alcohol and the dihydroergot alkaloids dilate only limited regions of the circulatory system. The hydrogenated ergot alkaloids, in addition to the peripheral, sympatholytic effect, inhibit the central regulation of circulation; they can be used for therapy of peripheral circulatory disorders. The centrally induced vasodilatation resulting from alcohol is one reason why patients with intermittent claudication, angina pectoris, and other circulatory ailments feel much better after ingestion of moderate quantities of alcohol. The physician should perhaps consider if under such circumstances ethyl alcohol should be considered and used as a pharmacological agent. (Concerning the vasodilating effects of pyrogen, see p. 145.)

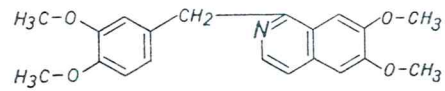
Smooth Muscle

Smooth muscle can be influenced pharmacologically in two ways: (1) by an influence on the autonomic nervous system including the transmitter substance and corresponding receptors (the pharmacological effects then depend on the activity of the sympathetic or the parasympathetic system at the target organ—these concepts are discussed in detail in the section on the autonomic nervous system) and (2) by affecting the smooth muscle cell directly. Compounds that act on the smooth muscle independent of the autonomic nervous system do not require the mediation of autonomic nerves, transmitter substances, or receptors. Consequently, they are not competitive antagonists to acetylcholine, norepinephrine, and their neurotransmitter analogs. Compounds that stimulate smooth muscle tone and inhibitory agents (spasmolytics) are both known.

Agents That Inhibit Smooth Muscle (Spasmolytics)

Papaverine

Papaverine is an alkaloid found in opium in concentrations of approximately 1%. Like morphine, it is structurally related to isoquinoline (cf. p. 146) but lacks



Papaverine

central effects. Papaverine relaxes smooth muscle independent of its autonomic innervation. Thus, vascular muscles, including those of the coronary and cerebral vessels, musculature of the bile and urinary ducts, and bronchial and intestinal muscles respond to papaverine with a decrease in tone. This action is especially pronounced in spasms (i.e., an initially very high tonus) of smooth muscles. Figure vessels, musculature of the bile and urinary ducts, and bronchial and intestinal muscles respond to papaverine with a decrease in tone. This action is especially pronounced in spasms (i.e., an initially very high tonus) of smooth muscles. Figure 20 shows the abolition by papaverine of a barium ion-induced spasm in isolated intestinal muscle.

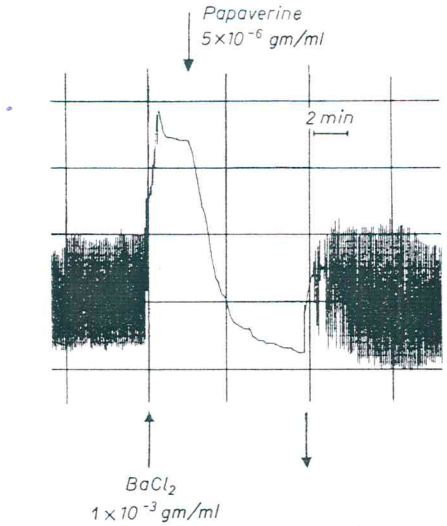


Fig. 20. The influence of barium ions and papaverine upon the pendulatory movements of the rabbit jejunum. Isotonic recording with a mechanoelectrical transducer connected to a recorder. Barium ions cause stimulation; papaverine acts as a spasmolytic.

Papaverine can be applied to therapy in conditions of increased smooth muscle tone, such as gastrointestinal cramps, and spasms affecting the uterus, the bronchi, the bile duct, and the urinary ducts. Although papaverine is absorbed from the gastrointestinal tract, parenteral or rectal administration is preferable; the dose level is between 0.05 and 0.2 gm several times daily. Intravenous injection should be carried out slowly in order to avoid unpleasant cardiovascular side effects. Papaverine has a quinidinelike effect on heart muscle (decreased rate of conduction, increase of the refractory period, and eventually arrythmia) and lowers blood pressure owing to peripheral vasodilatation. This general vasodepression may lead to a worsening of the condition in peripheral circulatory disorders in spite of a maximal distension of the vessels in the affected region. After chronic administration of papaverine, disturbances of liver function have been observed.

Apart from the alkaloid papaverine, there are synthetic substances which relax smooth muscle. α-[*N*-(β-diethylaminoethyl)-amino]-2-phenylacetic acid isoamyl ester, for instance, is clinically used like papaverine. The "nitrites" are equally capable of lowering the tone of smooth muscle. Their action is discussed on page 76. Sodium nitroprusside also relaxes vascular smooth muscle and provokes an acute fall in blood pressure (see p. 56). The intraarterial injection of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) leads to brief vasodilatation in the related muscles; adenosine also has a similar action. Nicotinic acid dilates only the dermal blood vessels after intraarterial injection.

Agents That Stimulate Smooth Muscle

Hormones from the Posterior Lobe of the Pituitary Gland

Both posterior pituitary hormones, oxytocin and vasopressin, directly stimulate smooth muscle. The effect of oxytocin is mainly restricted to the uterus; the compound thus has great physiological importance apart from its pharmacological use. Vasopressin has a nonspecific stimulatory action on all smooth muscle. The physiological importance of vasopressin does not appear to be based on this effect, but rather on its influence on kidney function (cf. p. 105).

Oxytocin

Oxytocin is an oligopeptide consisting of eight amino acids of which five are contained in a ring. The synthesis of the peptide is possible and is used for the industrial manufacture of oxytocin preparations (formula, p. 212). Oxytocin stimulates the smooth muscle of the uterus *in vivo* and *in vitro*. Uterine sensitivity is quite variable and depends on a number of factors: species characteristics, hormonal condition, and its functional state (phase of pregnancy). Low concentrations of oxytocin generate rhythmic contractions, whereas high doses can lead to prolonged contraction of the uterus. The sensitivity toward oxytocin changes over the period of pregnancy, being very low initially, rising as pregnancy progresses and reaching a maximum about the time of birth. It is not yet completely clear whether the increased sensitivity to oxytocin, and the increased

oxytocin concentration in the blood at the end of pregnancy are determining factors in the initiation of birth.

Since oxytocin is quickly destroyed in the intestinal tract, it must be given parenterally. Also in blood there is fast degradation by peptidases, so that the effect of an injection is only transient. Therefore, it is usually preferable to give oxytocin as an infusion over a longer period of time. Prior to the availability of the pure chemical compound, an international unit was based on a standard pituitary powder; 450–500 of these units correspond at present to 1 mg of pure oxytocin. The clinical dose is 1–3 units for a single injection or 0.005–0.02 units per minute for an infusion. Intranasal or transbuccal administration is also possible, but proper dosing is difficult. The indications for the use of oxytocin are based on the increased sensitivity of the uterus close to the time of birth: to initiate birth, increase uterine contractions if they are feeble, contract the uterus after a Cesarean section, and to stop postpartum bleedings from an atonic uterus. The administration of high oxytocin doses at the beginning of the birth process cannot be recommended.

Apart from the uterus, there is an action by oxytocin on the mammary glands (myoepithelium mammae). It stimulates the ejection of milk present in the glands, but the production of milk is not enhanced (galactokinetic action).

Vasopressin

Only the stimulatory effect of injected vasopressin on smooth muscle is discussed here (cf. additionally p. 105).

Administration of vasopressin increases blood pressure by vasoconstriction. Intestinal tonus and peristalsis are increased, as is the tonus of the biliary duct and the ureters. Coronary vessels behave like all other vessels: vasopressin causes coronary vasoconstriction. The possible precipitation of angina pectoris limits the use of vasopressin as a smooth muscle stimulant. However, it may be used cautiously for the following indications: in postoperative or pharmacologically induced paralytic ileus, in bladder atonia, in paralytic vascular collapse when combined with sympathomimetics in a slow infusion, or especially in types of collapse that do not respond to sympathomimetics alone. Vasopressin, as well as oxytocin, has no direct influence on cardiac and skeletal muscle. The dose of vasopressin necessary to stimulate smooth muscle is higher than the amount required for antidiuretic activity. Three to ten international units (IU) are usually required and thus exceed the amounts released from the posterior pituitary gland.

Ergot Alkaloids

Claviceps purpurea, a parasitic fungus growing on ears of grain, contains alkaloids closely related to each other as derivatives of lysergic acid, besides several biogenic amines. The following alkaloids have therapeutic importance: ergonovine, ergotamine, ergotoxine, and the semisynthetic methylergonovine, which contains a 2-aminobutanol group instead of the 2-aminopropanol moiety in the natural product.

Mode of Action

Ergotamine and the alkaloids of the ergotoxine group (ergocristine, ergocryptine, and ergocornine) have qualitatively the same effects. Ergonovine differs in some aspects from the others. Ergotamine stimulates the smooth muscle of the uterus and blood vessels.

Other organs with smooth muscle (e.g., bronchi and intestine) are scarcely affected. The effect on the uterus is concentration-dependent. Small doses cause rhythmic contractions or increase the frequency of an existing rhythm; the relaxation between contractions is still complete. High doses do not allow a period of relaxation since contractions are too closely spaced; this is called a tetanic uterine contraction (Fig. 21). The effect can be demonstrated both *in vivo* and *in vitro*. The sensitivity of the uterus toward ergot alkaloids, as with oxytocin, is strongly dependent on its functional state, with the highest sensitivity at the time of birth. Ergonovine possesses a stronger action than ergotamine on the uterus; parenteral administration results in an immediate reaction of the uterine musculature, while there is a latent period following the injection of ergotamine.

Ergonovine and methylergonovine are quickly and completely absorbed from the intestinal tract. The absorption of ergotamine is incomplete and takes much longer. The oral dose thus is five to ten times the amount given parenterally. The action of all ergot alkaloids fades only after a period of hours. The activity of the ergotoxine group is somewhat weaker than that of ergotamine

Ergotamine stimulates the vascular musculature. This acute vasoconstrictor effect appears with doses affecting the uterus and causes blood pressure elevation

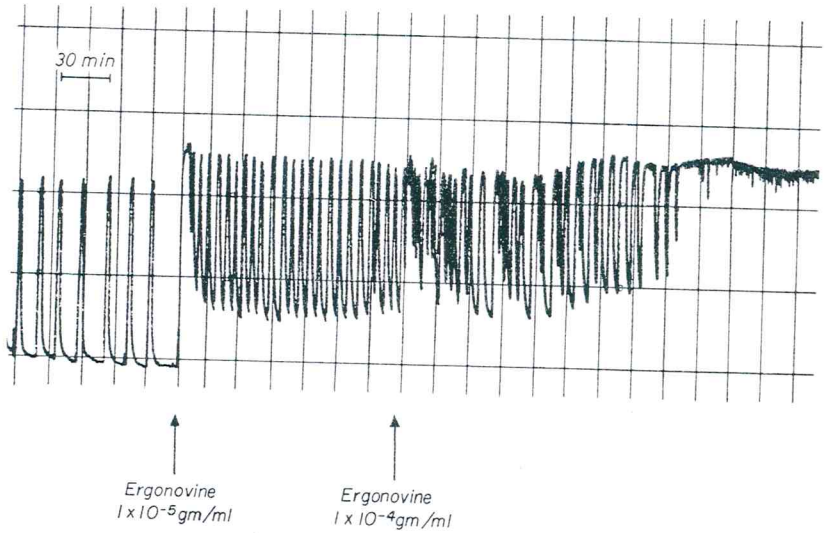
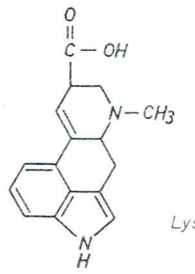
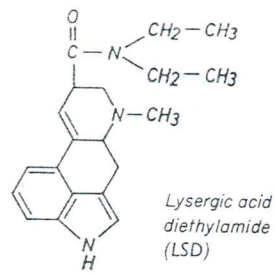


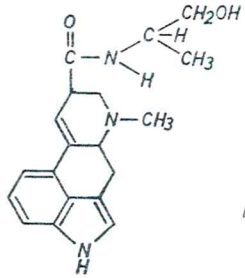
Fig. 21. The effect of ergonovine on the mechanical activity of the isolated guinea pig uterus. Isotonic recordings with a mechanoelectrical transducer connected to a recorder. Ergonovine stimulates uterine activity; in higher concentrations it results in a uterine contracture.



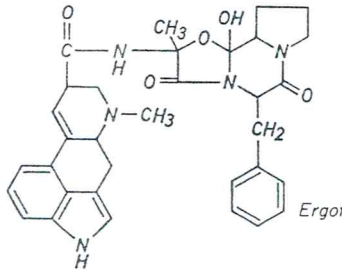
Lysergic acid



Lysergic acid diethylamide (LSD)



Ergonovine



Ergotamine

due to contraction of peripheral vessels. This pressor effect should be taken into account when ergotamine is used in obstetrics. The vasoconstrictor activities of ergonovine and methylergonovine are less pronounced; therapeutic doses do not change peripheral blood flow. The chronic use of ergotamine may damage the extremities as a result of constant vasoconstriction. In extreme cases the tissue becomes gangrenous. The damage appears to be caused not only by the constant stimulation of the smooth muscle but is aggravated by swelling of the endothelium and finally the formation of thrombi. The gangrene-inducing activity of ergot preparations is used for their biological assay, the cock's comb being especially sensitive. Gangrene resulting from chronic administration of ergot has become rare in modern times due to a purification of contaminated grain prior to its use as food. Epidemic mass poisonings occurred in earlier times. Acute cases of ergot poisoning, apart from vasoconstriction and severe diarrhea, are marked by central nervous system symptoms as well: headaches, nausea, vertigo, confusion, and hemiplegia.

Indications

Ergot alkaloids are suitable for bringing about a long-lasting contraction of the uterus after delivery. The outstanding indication is thus uterine atonia postpartum: bleeding after expulsion of the placenta, lochioschesis and incomplete involution. The ergot alkaloids are of less value in the suppression of uterine bleeding in the absence of pregnancy, since the muscle is then much less sensitive. They should

not be used to induce contractions at the beginning of birth, because of the danger of tetanic uterine contraction. The danger is supposedly less with methylergonovine than with ergotamine, and very cautious therapy with small doses of methylergonovine is sometimes recommended when oxytocin fails.

The use of galenic preparations is obsolete because of great variability in the content of active material and uncertain absorption. Methylergonovine is preferred to most other ergot alkaloids since it has a relatively favorable therapeutic index. The parenteral or oral dosage is from 0.05 to 0.2 mg.

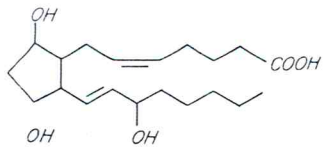
Vascular diseases and hypertension are contraindications to the use of ergot alkaloids. The drugs should also be avoided if liver and kidney disease is present. If methylergonovine is given during childbirth (which should not be done) it must be positively ascertained that there is no mechanical obstacle to parturition.

Action on the Autonomic Nervous System

Ergotamine, ergotoxine, and the dihydro derivatives, but not ergonovine, have a sympatholytic action due to blockade of α-receptors. This property of some of the ergot alkaloids was discussed in the section on sympatholytic agents (cf. p. 33). It should be pointed out that ergotamine has two opposing actions on the vessels: (1) direct muscle stimulation leading to vasoconstriction and (2) vasodilatation due to the sympatholytic effect. Which of the two actions predominates is dependent on the circumstances. The vasodilator component is the more difficult one to elicit; thus ergotamine is not used clinically as a vasodilator substance. More effective are the dihydro alkaloids, since these drugs stimulate smooth muscle to a much lesser degree so that the sympatholytic component clearly predominates. Apart from this purely peripheral activity, there is an additional vasodilator effect that is mediated by influencing central vascular regulation (cf. p. 42).

Prostaglandins

Prostaglandins are a group of cyclic, unsaturated fatty acids originally found in seminal fluid, but occurring in many tissues. Their physiological function is not clear. They act on smooth muscle in a variety of ways. In addition, they inhibit spontaneous lipolysis and lipolysis stimulated by catecholamines, glucagon, or theophylline. Prostaglandin $F_{2\alpha}$, and with an even more marked activity, E_2 provoke upon long-lasting infusion (rapid degradation in the lungs) rhythmic contractions of the pregnant human uterus. In this manner pregnancy can be interrupted in any stage. If the uterine contractions are too feeble, delivery will be accelerated by prostaglandins. In animal experiments prostaglandin E_2 administered as an aerosol causes bronchodilation.



Quinine

Low concentrations of quinine increase the excitability of the uterus to stimulating compounds such as oxytocin; quinine itself does not elicit contractions. Higher concentrations inhibit the uterine musculature. Only inhibition of the smooth muscle of other organs (as well as cardiac and skeletal muscle) is observed. Doses that lead to systemic poisoning may also induce an abortion.

Barium Ions

Barium is not used in therapy. Barium salts are utilized in experimental pharmacology to increase the tonus of smooth muscle, which can then be abolished by papaverine and similar drugs (Fig. 20). Apart from such tonic action on smooth muscle, there is a digitalislike toxic effect on the heart muscle. The excitability of skeletal muscle and the nervous system is augmented. In a number of tissues this effect may be caused by a displacement of calcium (specifically bound to the cell membrane) by barium, which is chemically similar. The cell membrane then reacts as in calcium deficiency. It is hyperexcitable.

Barium sulfate is practically insoluble in water and therefore not poisonous. It is used as an X-ray contrast agent. Since low quantities of 0.5–1.0 gm of soluble barium salts may be lethal, barium sulfate given in large doses must be very pure. The therapy of barium poisoning is symptomatic (spasmolytics, morphine, and parasympatholytics). Barium ions that are still contained within the gastrointestinal tract can be precipitated by oral administration of sulfate (sodium or magnesium sulfate), thus preventing further absorption.

Biogenic Amines

Besides the biogenic amines, norepinephrine and epinephrine, which have already been discussed, histamine and serotonin are of pharmacological importance. Furthermore, dopamine has a function in the brain.

HISTAMINE. Histamine is widely distributed in nature, both in plants (e.g., *Claviceps purpurea* and the stinging nettle) and in the animal kingdom. For example, it is present in the secretion of stinging insects. Tissues of mammals contain varying amounts of histamine in which the distribution among the various tissues is specific for the species. In humans the highest concentration of histamine is found in the lungs, the skin, and the gastrointestinal tract (approximately 0.01 mg/gm tissue). The amine is stored as a biologically inactive form in basophilic leukocytes and in tissue mast cells, which also contain large amounts of heparin.

Histamine is formed from the amino acid, histidine, in the cells themselves by a histidine decarboxylase. α-Methylhistidine competitively inhibits this decarboxylation and hence the formation of histamine. Histamine is rapidly degraded by a diamine oxidase (histaminase), enzymic acetylation, or *N*-methylation in the imidazole ring.

Pharmacological Actions. Histamine has a direct, stimulatory effect on some smooth muscle. Thus the bronchial, uterine, and intestinal musculature react with a contraction. The bronchoconstricting effect of histamine is of especial

interest in the pathophysiology of allergic asthma. In contrast, the vascular muscles *in vivo* relax in the presence of histamine. This vasodilator effect is the reason for the fall in blood pressure and the headache after parenteral administration of histamine (see Fig. 3). Cardiac and skeletal muscle are relatively insensitive to histamine.

Histamine dilates the capillaries and increases their permeability considerably, allowing plasma to escape from the vascular bed into tissues. Morphologically a loosening of the intracellular substance of the endothelium is observed. Edema develops and may be accompanied by increased viscosity of the blood. The mechanism which is responsible for this increased permeability is as yet unknown. Glands of the gastric mucosa are strongly stimulated by histamine. This increased secretion is independent of innervation and is resistant to antihistaminics and atropine. On intracutaneous administration of histamine (stinging nettle, insects, or injection) an itching weal and a painful redness of the skin (capillary dilation) develops, which is edematous because of the increased permeability. The edema may be so severe that blisters are formed.

Histamine not stored in mast cells seems to possess physiological importance in relation to the rapid growth of embryonic and wound tissue and of tumor cells. It is not clear whether the activity of histamine in increasing permeability is necessary to ensure the transport of materials through cell membranes.

Histamine has no therapeutic use. For the diagnosis of various kinds of achlorhydria, especially in suspected pernicious anemia, the histamine analog, betazole [3-(β-aminoethyl)pyrazole], or gastrin are used instead because of lesser side effects.

Release of Histamine. Histamine, stored inside cells where it is biologically inactive and protected from degradation, can be released from that bound state. The most primitive method of release for histamine is cell destruction, such as that occurring with large wounds. Another process that leads to the liberation of histamine is the allergic reaction, whose symptoms whether occurring locally or generally are largely caused by the released histamine. Pharmacological agents also can cause the release of histamine. Thus, some side effects of *d*-tubocurarine (fall in blood pressure, bronchial spasms, and glottal edema) are caused by endogenous histamine. An extremely potent liberator, compound 48/80, formed by condensation of *p*-methoxyphenylethylmethylamine with formaldehyde, is used frequently in experimental research. Histamine stores can be completely depleted by 48/80 with the release of preformed histamine; the rapid decarboxylation of histidine contributes to the elevation of the histamine level.

ANTIHISTAMINES. Antihistamines are compounds that to varying degrees are capable of inhibiting the effects of histamine. Their site of action is the histamine receptor in the tissue, which is blocked competitively, so that histamine is no longer able to react at the receptor site (see also Fig. 22). They do not affect the degradation or release of histamine. Their affinity for the receptors is ascribable to their structural relationship to histamine as is easily seen from their basic structure (see the formulas on p. 52).

Optimal antihistaminic activity is achieved if both substituents on the nitrogen are methyl groups. X may be either another nitrogen, an oxygen, or a carbon

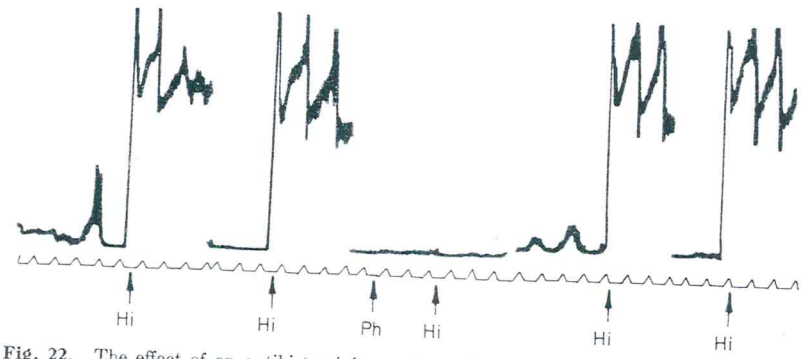


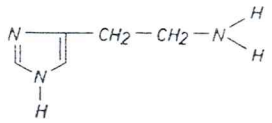
Fig. 22. The effect of an antihistaminic agent on the response to histamine of the isolated guinea pig intestine. Hi, histamine 2×10^{-7} gm/ml; Ph, pheniramine 2×10^{-6} gm/ml. The stimulating effect of histamine is abolished in the presence of pheniramine.

atom. The substituents R_1 and R_2 (the "nucleus" of the antihistamine) must be rather large aryl or arylalkyl groups or equivalent polycyclic ring systems. These moieties of the molecule determine the secondary properties of the antihistaminic agent. The basic structure may be contained completely within a ring system, without loss of biological activity. Some typical examples are given in the collection of structural formulas.

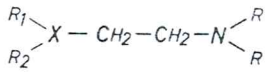
Using the above general principles, many compounds have been synthesized and are recognized as effective antihistaminic agents. Therapeutically only a few of them are used. The indication for antihistamines is based on their mechanism of action; they are called for in any condition that leads to the release of histamine; that is, primarily in allergic reactions (urticaria, angioneurotic edema, hay fever, serum sickness, drug hypersensitivity, and sometimes also in bronchial asthma). The choice of drug depends principally on the side effects of the individual agents. The central nervous system is depressed by some antihistamines and is stimulated by others. Individual sensitivity is quite variable. Disturbances may occur within the autonomic nervous system, leading to angina pectoris, gastrointestinal complaints, or problems in micturition. Some antihistamines have a weak local anesthetic effect. Topically applied, they are useful in allergic itching of the skin.

Effects similar to those of atropine and quinidine have also been described. If sedative side effects are desired, promethazine and tripelennamine can be recommended. Other preparations are not active as sedatives or have a slight stimulatory effect. These are preferable for people who have to remain alert because of their professional activity or when driving a vehicle. An example is 3-methyl-9-benzyl-1,2,3,4-tetrahydro-γ-carboline. Single doses for adults are between 25 and 100 mg and oral administration is sufficient in most cases. Only in cases of allergic shock is an intramuscular (or intravenous) injection indicated.

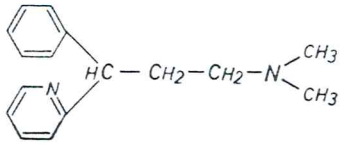
Some histamine antagonists with particularly high activity as central nervous system depressants can be used as excellent antiemetics (cf. p. 167). The sedative effect may further be utilized in premedications for anesthesia or to calm extremely



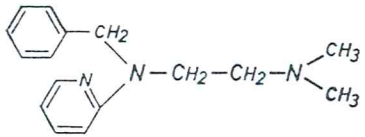
Histamine
2-(4-Imidazolyl)-ethylamine



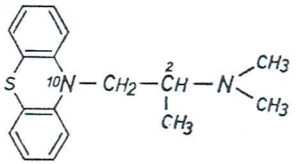
Basic structure of antihistamines (see the text)



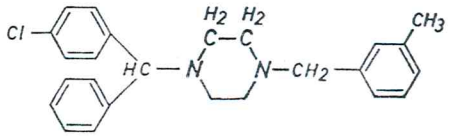
Pheniramine
2-[α-(2-Dimethylaminoethyl) benzyl]pyridine



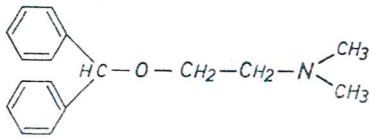
Tripelennamine
2-[Benzyl(2-dimethylaminoethyl) amino]pyridine



Promethazine
10-(2-Dimethylaminopropyl)-phenothiazine



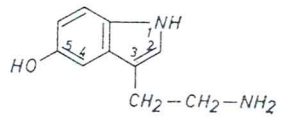
Meclizine
1-(p-Chloro-α-phenylbenzyl)-4-(m-methylbenzyl)piperazine



Diphenhydramine
2-Diphenylmethoxy-N,N-dimethylethylamine

agitated subjects (promethazine). The central effects, which are often undesirable in antihistamines, may deliberately be emphasized by chemical modifications of the molecule. This has led to the development of a number of psychopharmacological agents (cf. p. 192).

SEROTONIN. In primitive as well as highly developed species, including man, an additional biogenic amine is found, namely, serotonin (5-hydroxytryptamine, enteramine). It is formed by hydroxylation and decarboxylation of the amino acid tryptophan, and is degraded by monoamine oxidase to 5-hydroxyindoleacetic acid, which is then excreted. Some cells, such as the enterochromaffin cells of the intestine, contain serotonin in extremely high concentration. A neoplastic dedifferentiation of these cells is called a carcinoid and is characterized by periodic flooding of the organism with serotonin and kallikrein. Symptoms are vasomotor reactions (flushing), asthmalike attacks, diarrhea, and in addition pathological changes in the endocardium of unclear origin. The high serotonin content of some brain areas



Serotonin
3-(2-Aminoethyl)-5-indolol, 5-Hydroxytryptamine

(hypothalamus, mesencephalon, caudate nucleus, and the base of the fourth ventricle) is noteworthy and has led to speculations on the physiological role of this amine, especially since other indole derivatives elicit remarkable effects in the central nervous system (cf. psychotomimetics, p. 189). Similarly, thrombocytes contain high quantities of serotonin. Along with the tissue noradrenaline stores, the serotonin stores are partially or completely depleted by reserpine. Monoamine oxidase inhibitors impair the degradation of serotonin, so that the tissue concentration rises. Since reserpine as well as monoamine oxidase inhibitors are used as psychopharmacological agents, their interaction with serotonin is an additional indication for the important role of this compound in the central nervous system.

The pharmacological action of serotonin consists primarily in the stimulation of smooth muscle; *in vitro*, blood vessels, bronchi, intestine, and the uterus contract after the addition of low concentrations of 5-hydroxytryptamine. The blood pressure is increased after intravenous injection due to vasoconstriction while on the other hand long-lasting infusion results in a lowering of the pressure. The explanation is the elicitation of the Bezold-Jarisch reflex, which is also observed after veratrum alkaloids (e.g., protoveratrine). The individual response of the circulatory system depends largely on its initial state. Skeletal and cardiac muscle, as well as other tissues, are scarcely affected by any direct action of serotonin. The stimulating effect on smooth muscle can be counteracted effectively by rather specific antagonists of serotonin, such as lysergic acid diethylamide, 2,5-dimethylserotonin, methysergide [1-methyl-lysergic acid-(2′butanol-1′)amide], and cyproheptadine [1-methyl-4-(5-dibenzo-a,e-cycloheptatrienylidene)piperidine]. The last two compounds are used in the therapy of migraine. After administration of methysergide, certain unusual side effects may appear which are not of a serious nature and

despite continued administration eventually disappear. However, fibrotic narrowing of blood vessels may also occur, which results in serious complications. For this reason the drug is contraindicated in all cases of vascular disease. After prolonged administration, fibrotic changes in various parts of the organism are observed, mainly in the retroperitoneal area but also in the heart and pleura. Cyproheptadine has, in addition, antihistaminic and mild atropinelike effects, which explains some of its side effects. The appetite-stimulating action of these compounds remains so far unexplained.

Peptides

Well-defined peptides contained in tissues and serum are liberated under certain conditions and are then pharmacologically active. Some peptides whose structures are known are discussed briefly below. In the future, the peptides and the possibility of blocking their release or of inhibiting their activity may become of therapeutic importance.

BRADYKININ. Bradykinin, similar to other kinins, is cleaved from its precursor plasma protein by proteolytic enzymes such as plasmin, trypsin, and snake venom. It is an unbranched nonapeptide of the following composition:

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg

Bradykinin

It is identical with kallidin (kinin) 9 which along with the even more potent vasoactive kallidin (kinin) 10, a decapeptide, is liberated from α-globulins by the protease activity of kallikrein. Bradykinin causes pain and acts on smooth muscle. The response of most of the organs with smooth muscle is stimulatory, e.g., the intestine and bronchi. The vessels, on the other hand, are dilated, and their permeability increases simultaneously. The kinins may play a role in allergic and anaphylactic reactions since they elicit analogous effects when exogenous material is intentionally administered.

ANGIOTENSIN (HYPERTENSIN). Under certain conditions a substance called renin is released from the juxtaglomerular cells of the kidney (cf. p. 96). This compound converts a precursor in the plasma to angiotensin I which is in turn converted to angiotensin II. The angiotensins are unbranched peptides with 8 or 10 amino acids in the chain.

Asp-Arg-Val-Tyr-Ileu-His-Pro-Phe-His-Leu

Angiotensin I

Asp-Arg-Val-Tyr-Ileu-His-Pro-Phe

Angiotensin II

The structural formulas above correspond to angiotensins isolated from horse

serum. The compounds obtained from bovine serum differ by one amino acid; valine replaces isoleucine.

The angiotensins have extraordinarily potent vasoconstrictor activity. Quantities from 0.005 to 0.01 mg given intravenously to humans result in a definite increase in blood pressure. The effect disappears within a few minutes and the release of norepinephrine is involved as well. Secretion of water and salt is diminished by angiotensins. The mechanism for this effect is discussed in greater detail on page 96. It has been proposed that a renin–angiotensin mechanism may possibly be involved in the blood pressure elevation that accompanies kidney diseases. A commercial preparation which is used instead of epinephrine to raise the blood pressure is angiotensinamide.

Appendix on Therapeutics

Bronchial Asthma

It is frequently necessary to use agents from various pharmacological classes, together or in turn, for the treatment of bronchial asthma. Since this ailment appears to be highly dependent on psychological influences, placebos elicit favorable although transient responses in up to 40% of all cases. On the other hand, this also means that an improvement may be achieved with tranquilizers as a result of a "psychoautonomic uncoupling." An acute asthma attack is best treated with epinephrine or epinephrinelike compounds. Doses of 0.5 (up to 0.8) mg of epinephrine are injected intramuscularly or preferably inhaled. In most cases the inhalation of isoproterenol solutions is effective, with 3–8 drops of a 1% solution being converted to an aerosol in a hand atomizer. The danger of severe cardiac toxicity should be reemphasized. The same drug can also be administered sublingually in doses of 10–20 mg several times a day. Orciprenaline, which is closely related, has a longer duration of action and can be administered orally. In general the clinical experience with this drug is more favorable.

Sometimes the parenteral administration of calcium or theophylline-containing preparations intravenously or rectally (for instance, aminophylline) is effective. In such therapy, not only is there a broncholytic effect, but a central stimulatory action is involved as well. Despite the frequently elevated vagal tone, atropine is effective in only a few cases. Antihistamines also generally have an unsatisfactory effect. Ephedrine may be useful for children. Morphine or morphine analogs, which are still recommended by some, have no place in asthma therapy because the depression of the respiratory center leads to further deterioration of the oxygen supply. If a disruption of psychoautonomic mechanisms is desired, the "psychoautonomic uncoupling" activity of tranquilizers or, if necessary, chlorpromazinelike drugs which do not inhibit respiration should be utilized.

Glucocorticoids, such as prednisone or prednisolone, often give excellent re-

sponses in cases of severe chronic bronchial asthma, but the dosage should be reduced as soon as possible and chronic treatment should be avoided. In cases of status asthmaticus, extreme sedation of the patient in the sense of a functional "autonomic decentralization" must first be obtained. Then, an intravenous injection of 25 mg of prednisolone sodium succinate can be life-saving. Such a treatment may be preceded by a very slow intravenous infusion of 0.5 gm of aminophylline or 0.5 mg of epinephrine. Respiratory acidosis and the always menacing right-sided cardiac insufficiency are treated correspondingly.

Hypertension

It has become possible, with a combination of drugs having different modes of action, to attain such a successful drug regimen for the therapy of hypertension that in many cases a considerable prolongation of life will be achieved. However, consistent drug treatment is necessary. Basically, the treatment of essential and renal hypertension is the same. However, the extent to which the blood pressure is elevated plays a role in the choice of drugs. In essential hypertension the use of "psychoautonomic uncoupling" drugs and restricted salt intake are useful "preliminary" measures.

In addition to the dietary restrictions, saluretics of the benzothiadiazine group are currently given in all cases of hypertension. In mild cases of the disease, these agents alone are sufficient, for example, chlorthalidone (100 mg) twice or three times a week (orally). If this therapeutic regimen does not lead to success, additional agents with a different mode of action should be chosen, such as reserpine or, when this is not sufficient, a combination of reserpine with dihydralazine. In these combinations much smaller doses of the individual compounds are required, so that their side effects are diminished. The saluretics mentioned above potentiate the effect of all other antihypertensive agents and reestablish a possibly diminished sensitivity to them. The daily doses of reserpine alone are 0.25–1 mg and of dihydralazine alone, 50–100 mg; in combination, quantities of 0.3 mg of reserpine and 30 mg of dihydralazine are sufficient. α-Methyldopa, which has a different mechanism of action, may be given in daily doses of 0.5–3.0 gm combination with a saluretic agent if the above treatment is not satisfactory. Side effects are relatively slight. Clonidine lowers the blood pressure to about the same extent as α-methyldopa after daily oral doses of 0.15–1.2 mg. Only if the above-mentioned drugs do not achieve results should the adrenergic neuron-blocking agent guanethidine be taken into consideration. The dosage begins at 10 mg daily and may be increased until 30–60 mg by mouth. Ganglionic blocking agents are only indicated for the treatment of acute, life-menacing hypertensive crises. For the same purpose sodium nitroprusside may be infused intravenously. The effect occurs immediately and after discontinuation of the drug rapidly ceases (dosage, individually, 0.02–0.4 mg/min).

Long term administration of β-adrenergic blocking agents also has proved useful in special cases of hypertension, especially if the disease is accompanied by tachycardia without cardiac insufficiency (e.g., propranolol in daily doses between 30 and 300 mg).

Migraine

Since the cause of migraine is imperfectly understood, and various pathological pictures may appear during a single attack of migraine, treatment is difficult. Mild attacks can be moderated by large doses of the usual analgesics, such as aminopyrine or phenacetin. Since, according to the present view, the pain in migraine is caused by a dilation of cerebral vessels (not by a spasm, as had been assumed earlier), it seems preferable to utilize drugs which cause constriction of these vessels. For this purpose ergotamine, alone or in combination with caffeine, is given. In severe attacks, especially if they are accompanied by vomiting, 0.5 mg ergotamine tartrate, repeated when necessary is injected subcutaneously. Dihydroergotamine appears to be insufficiently active. There exist arguments in favor of the assumption that serotonin is involved in the development of a migraine incident since the therapeutic effect of serotonin antagonists, especially methysergide and also cyproheptadine, has often been demonstrated. Prophylaxis is more effective than the attempt to combat an attack of migraine or its equivalent. The side effects of the serotonin antagonists have been enumerated above.

The Heart

Compounds with a Positive Inotropic Effect

Cardiac Glycosides

The term cardiac glycosides applies to compounds possessing well-defined pharmacological and chemical properties. Pharmacologically they are characterized by a positive inotropic effect and chemically by a very specific structure consisting of a steroid moiety, an unsaturated lactone ring, and saccharide units connected by ether bonds.

Occurrence

Cardiac glycosides have been found in various plants, such as *Digitalis purpurea, Digitalis lanata* (foxglove), *Strophanthus kombe, Strophanthus gratus, Urginea* (Scilla) *maritima* (squill, sea onion), *Adonis vernalis,* and *Convallaria majalis* (lily of the valley). A total of more than 200 glycosides with cardiac activity is known. The foxglove contains the cardiac glycosides bound to one molecule of glucose (*D. purpurea*) or to one molecule of glucose and one of acetic acid (*D. lanata*). These are the native glycosides. The cardiac glycoside itself consists of an aglycone (genin) and some saccharide units.

TABLE II

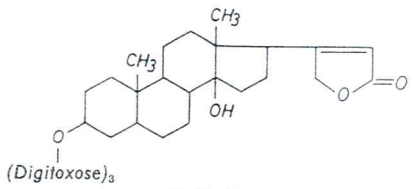
Composition of Some Cardiac Glycosides

Native glycoside	minus sugar	Is identical to	Glycoside
Purpea-glycoside A	– glucose	=	Digitoxin
Purpea-glycoside B	– glucose	=	Gitoxin
Lanatoside A	– (glucose + acetic acid)	=	Digitoxin
Lanatoside B	– (glucose + acetic acid)	=	Gitoxin
Lanatoside C	– (glucose + acetic acid)	=	Digoxin

Glycoside	minus sugars	Is identical to	Genin
Digitoxin	– 3 digitoxose	=	Digitoxigenin
Digoxin	– 3 digitoxose	=	Digoxigenin
k-Strophanthoside	– (2 glucose + 1 cymarose)	=	Strophanthidin
Scillaren A	– (1 glucose + 1 rhamnose)	=	Scillarenin A
g-Strophanthin (ouabain)	– 1 rhamnose	=	g-Strophanthidin (ouabagenin)

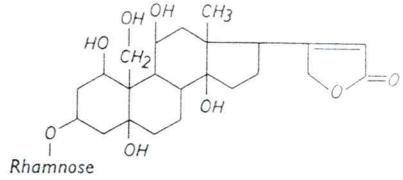
Chemical Structure

The structures of digitoxin, ouabain, and scillaren A are given below to illustrate the chemical composition of cardiac glycosides:

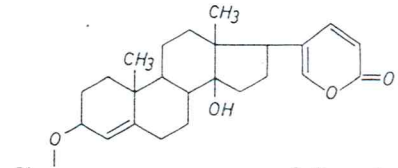


Digitoxin

5-membered lactone ring: cardenolide



g-Strophanthin (Ouabain)

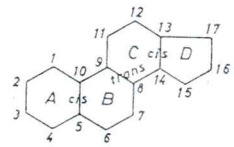


Scillaren A

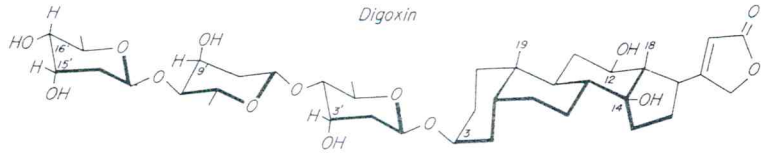
6-membered lactone ring: bufadienolide

Common to all cardiac glycosides is a steroid nucleus of a definite steric configuration with the following substituents: an OH group in position 3 which forms

an ether linkage with the sugar, an OH group in position 14, and an unsaturated lactone ring at position 17. Further substituents may be present at carbons 5, 10, 11, 12, or 17. Cardenolides (digitalis, strophanthus, and convallaria glycosides) and bufadienolides (scilla glycosides and toad poisons with cardiac activity) are differentiated by the size of the lactone ring (5- or 6-membered).



Additional conditions must be fulfilled before a steroid shows cardiac activity The fusion of the rings allows the existence of a number of stereoisomeric forms, namely trans- or cis fusion. The following sequence of ring fusions is characteristic for cardiac glycosides: AB cis (if A is saturated), BC trans, CD cis. This distinguishes the cardiac glycosides from other biologically active steroids, such as sex and adrenocortical hormones, and the bile acids. A further requirement for cardiac activity is a β-configuration for both the 17-lactone ring and the 3-hydroxyl group. The lactone ring must be unsaturated since dihydrogenated genins have much lower activity. The stereochemical arrangement of a cardiac glycoside is shown in the following figure.



The sugar moiety has no particular influence on the cardiac effect since sugar-free genins show similar positive inotropic activity to that of the glycosides. The sugars are of importance for the physicochemical behavior of the glycoside in the organism (absorption, distribution, binding, rate of degradation, etc.) and are therefore decisive for the therapeutic usage of the cardiac glycosides. Our present knowledge indicates two active centers in a glycoside molecule that are required for cardiac activity: (1) the carbonyl oxygen in the β-oriented lactone ring which must be strongly electronegative (a mesomeric effect due to conjugation with the double bond in the unsaturated ring system) and (2) the β-oriented oxygen in position 3. The fact that these two active groups are attached to a rigid molecule which practically fixes their position relative to one another may also be an additional factor involved in their high absolute activity.

The sugars isolated after hydrolysis of the glycosides are, with the exception of glucose, rare compounds which in some cases are found only in their combination with the cardiac glycosides.

Therapeutic Effect

The main effect of cardiac glycosides and their genins consists in an enhancement of the contractile force of cardiac muscle. This positive inotropic effect can be demonstrated *in vivo* and, in isolated heart tissue, *in vitro* as well. Figure 23 shows an experiment on the isolated guinea pig atrium to demonstrate the positive inotropic effect of ouabain (g-strophanthin). The magnitude of the positive inotropic effect depends on the amplitude of contraction in the heart muscle prior to addition of the glycoside or its genin. A well-contracting muscle will not show the same percentage increase in amplitude as a muscle that has an initially lower contractile amplitude. Thus the effect is best demonstrated on a failing heart

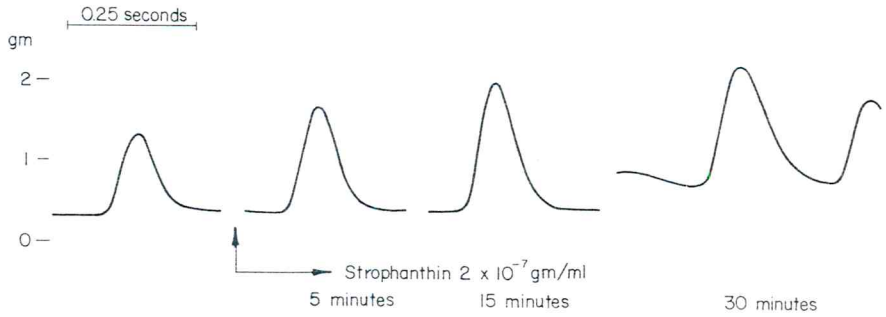


Fig. 23. The effect of ouabain (g-strophanthin) 2×10^{-7} gm/ml on the electrically stimulated, isolated guinea pig atrium. Contractions recorded by means of a strain gauge connected to a recorder. Note the rapid recorder speed. The positive ionotropic effect develops within 15 min of the addition of the glycoside. Contractile amplitude increases, the rate of tension development and rate of relaxation increase, the duration of each contraction remains constant. Toxicity develops after 30 min of drug exposure; relaxation velocity decreases, complete relaxation is no longer obtained, and additional spontaneous contractions occur as the result of the formation of ectopic foci.

muscle (Fig. 24). As a result of the positive inotropic effect, the failing heart is affected in the following manner. The amplitude and rate of contraction (see dp/dt in Fig. 24) increase. The chambers are emptied more completely and the size of the heart decreases.

The quantity of venous blood taken up during each diastole increases, and thus the venous pressure is lowered. The direct action on the heart is the actual therapeutic effect of cardiac glycosides.

In addition, this purely muscular phenomenon is favorably influenced by a decrease in cardiac frequency, which can occur during therapy with these glycosides. The filling time of the heart during diastole is increased by this effect, and the coronary circulation is also improved (during systole blood does not flow in the coronary circulation).

The negative chronotropic effect of therapeutic doses is principally the result of the improved state of the heart and circulation; the elevated central venous pres-

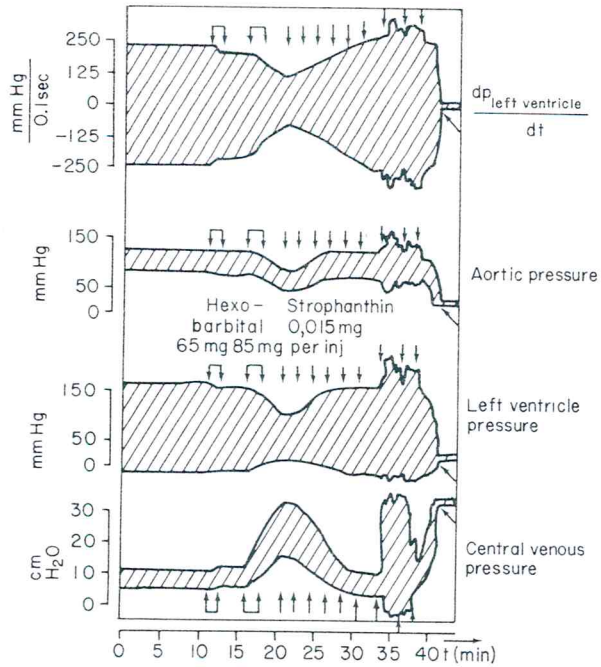


Fig. 24. Effect of ouabain on contractile activity of the heart in a heart–lung preparation of the cat (3.5 kg). Synchronous recording of the pressures via a transducer. The drugs were administered into the venous blood. The infusion of 150 mg hexobarbital over about 7 min causes myocardial insufficiency (note especially the change in central venous pressure) that would rapidly lead to complete cardiac failure in the absence of therapeutic measures. The administration of 5×0.015 mg ouabain over approximately 7 min reinstitutes cardiac work until the initial level is reached; an additional 0.015 mg of the glycoside causes a further increase of myocardial contractility (observe the rate of rise and fall of ventricular pressure, *dp/dt*). The additional administration of 3×0.015 mg ouabain causes cardiac irregularities and subsequently, cardiac arrest (↖).

sure with corresponding atrial stretching is depressed. A direct influence on the pacemaker frequency is only marginally demonstrable. Vagal tone is increased and also involved in the cardiac slowing. The effect on the conducting system is pronounced. The conduction velocity is decreased, and consequently AV conduction time is increased. (The ECG shows a longer PR interval). The refractory period of the heart muscle is shortened.

During the period of the positive inotropic effect, the heart performs more work without a corresponding increase in oxygen consumption. This phenomenon is described as an improvement in cardiac efficiency or energy utilization under the influence of cardiac glycosides.

The basic mechanism that underlies the positive inotropic effect of glycosides or their aglycones has not yet been elucidated completely. The following hypothetical

sites of action have been proposed: in cardiac metabolism, on the contractile proteins, in sodium-potassium distribution by means of an inhibition of membrane ATPase. Convincing experimental evidence is lacking for any of these hypotheses. Recent investigations with radioactive ions have placed intracellular calcium metabolism in the forefront of considerations of the mechanism of action of these glycosides. In the presence of therapeutic glycoside concentrations more labile calcium is available within the cell. This labile calcium results in a better activation of the contractile system during excitation. The increase of the labile Ca fraction is not, as is the case in the presence of epinephrine, caused by an enhanced Ca influx during the action potential. It cannot be decided yet whether there exists a causal relationship between the increase of the labile Ca fraction and ATPase inhibition.

Chronic cardiac insufficiency is accompanied by retention of water and sodium. During therapy with glycosides the retained water and salts are excreted. The diuretic effect is not the result of a direct action on the kidneys but rather the result of increased cardiac output and the consequent improvement in general circulation.

The therapeutic effect of cardiac glycosides is restricted exclusively to the heart; smooth or skeletal muscle, as well as parenchymatous organs, are not affected. The only extracardiac resorptive effect in therapeutic doses is vomiting caused by digitalis, which occurs in a relatively small percentage of patients. It results from an action of cardiac glycosides on the chemoreceptors in the dorsolateral vagal nucleus (area postrema of the medulla oblongata) and is therefore independent of the route of administration. Oral administration of cardiac glycosides will cause vomiting, nausea, epigastric pain, and diarrhea, more frequently owing to local irritation. Galenic preparations cause irritation of the mucous membranes in addition to these effects, owing to contaminating substances.

Toxicity

The therapeutic index of cardiac glycosides is small. Serious toxic symptoms appear if the full therapeutic dose is exceeded by 1.5–3 times. On the basis of different individual sensitivity, the onset of side effects (arrythmias, vomiting) may appear even before the full therapeutic effect has been attained. The toxic effects in man manifest themselves primarily on the heart. Experimental work has shown that glycosides have a detrimental effect on the functions of cell membranes. This action centers specifically on the "ion pumps" located in the membrane which function to maintain the potassium-sodium ion gradients. Cardiac glycosides inhibit this mechanism, and potassium is lost from the cell while sodium is taken up.

This effect has been demonstrated in many types of tissue from various animal species. In addition to this inhibition of the "ion pump," there appears to be an influence on the "passive" permeability of the cell membrane as well.

This influence on the membrane also can be observed in heart muscle but at concentrations higher than those necessary for the positive inotropic effect; such concentrations elicit toxic manifestations.

An example of the toxic action of cardiac glycosides or aglycones on heart muscle

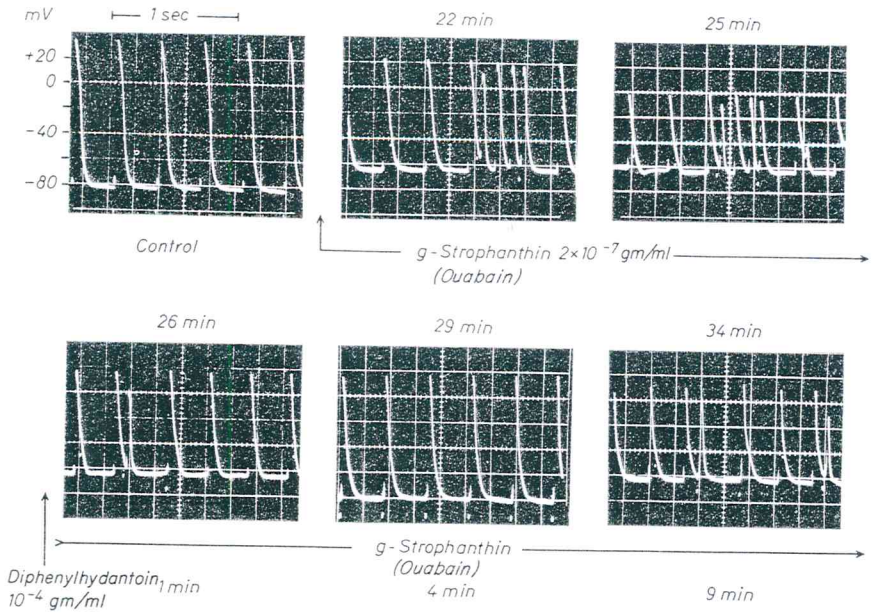


Fig. 25. The toxic effects of strophanthin on the cardiac cell membrane. Experiment on the isolated atrium of the guinea pig; recording of the action potential and membrane potential by means of intracellular microelectrodes. The preparation was stimulated at a constant frequency (4 Hz). The control recording shows a membrane potential of about −82 mV and an overshoot of about +30 mV. The organ bath was then perfused with a Tyrode solution containing a toxic concentration of strophanthin (2×10^{-7} gm/ml). The next two recordings demonstrate glycoside toxicity after 22 or 25 min of exposure through decrease in the membrane and overshoot potential, and instability of the membrane potential which is exhibited by the spontaneous action potentials. Between the third and fourth recording, diphenylhydantoin was injected into the bath, which was still being perfused with strophanthin-containing solution. The "electrical properties" of the membrane improved within a few minutes. The membrane potential was normalized, and the extra systoles disappeared. This effect of diphenylhydantoin occurs although strophanthin is still present. Following the washout of diphenylhydantoin, strophanthin intoxication again occurred (last recording).

is demonstrated in Fig. 23 with the isolated atrium. Two symptoms of poisoning can be recognized; irregularities and contracture. The disturbance in the electrical properties of the membrane are presumably caused by the effects of cardiac glycosides on ion permeability, as described above (see Fig. 25). The contracture of the heart muscle is possibly caused by flooding of intracellular spaces with calcium ions.

Glycoside intoxication is essentially the same *in vivo* as *in vitro*. Depending on the extent of the poisoning, depression of the ST segment, extra systoles (generally of ventricular origin), partial or total block, and tachycardia (in the most serious cases ventricular tachycardia) are observed. These arrhythmias are triggered by

the delayed spreading of excitation in the specific conducting system combined with the shortened refractory period of the muscle. Death is usually caused by ventricular fibrillation; upon autopsy the heart is found in a contracted state. The potassium content of the heart muscle is lowered, while that of sodium is elevated. In experimental animals, with glycoside intoxication of long duration (cumulation), morphologically demonstrable degenerative alterations of heart muscle cells, which are only partly reversible, are observed.

Apart from these cardiac symptoms extracardiac effects appear with poisoning. These effects may be slight on the central nervous system (drowsiness, nausea, headaches, chromatopsia, and neuralgia), but more serious symptoms may also develop (confusion, visual disturbances, hallucinations, delirium, and convulsions).

In this context it may be pointed out that the heart of some species is resistant to the effects of glycosides: rats do not die as a result of cardiac toxicity but of brain damage (paralysis of the respiratory center) after administration of high glycoside doses.

A number of other tissues show, *in vivo*, the ion-pump effect described above. Skeletal muscle (exhibited as muscle weakness) and erythrocytes lose potassium and take up sodium. Active transport phenomena are inhibited as well in the renal tubules. In toxic concentrations cardiac glycosides have a "saluretic" effect. However, as described above, the increased output of water and salt which takes place during the therapy of cardiac failure is dependent upon the action of the drug on the myocardium, not upon the kidneys.

Therapy of Poisoning by Cardiac Glycosides

The life of a patient poisoned by these glycosides is menaced by the above cardiac symptoms. Since the severity of the intoxication depends not only on the quantity of glycoside but also is directly proportional to the tissue concentration of calcium ions and inversely proportional to the tissue concentration of potassium ions, the following two "specific" measures can be recommended: infusion of potassium (approximately 0.3% potassium chloride in 5% glucose or fructose solution until 5.0 gm of potassium chloride have been given) and lowering of the calcium concentration by infusion of the sodium salt of ethylenediaminetetraacetic acid (EDTA) or by infusion of 3.8% sodium citrate solution. The maximal possible dose is limited by the appearance of symptoms of tetany. The treatment should be carried out under electrocardiographic (ECG) control and must be managed individually. In addition, symptomatic treatment may be considered: inhibition of vagal sensitization by atropine, use of compounds related to epinephrine in cases of heart block, intravenous procaine amide when ventricular fibrillation is imminent and sedation of the patient. More recent experience has shown that cardiac irregularities in glycoside-sensitive patients can be suppressed quite well by simultaneous administration of diphenylhydantoin. An example is shown by means of the animal experiment depicted in Fig. 25. The severe glycoside intoxication can be almost completely normalized by diphenylhydantoin. Doses of 0.1 to 0.2 gm orally per day are necessary as long as an acute effect is not required. If this is the case, a careful infusion can be performed. By prudent dosing which is just sufficient to abolish the membrane instability, the positive inotropic effect of glycoside is not, or only insignificantly attenuated. As a result of distribution phenomena the diphenylhydantoin level in the blood is reduced to zero within 1–2 hr, also after intravenous administration. Rapid injections of large doses of diphenylhydantoin (0.4–0.6 gm), however, damage the heart muscle.

Indications

Cardiac glycosides are unsurpassed for the treatment of cardiac insufficiency. However, the therapeutic success is highly dependent upon etiology of the insufficiency. Cases resulting from arteriosclerosis, hypertension, or valvular defects respond particularly well. Less favorable results are obtained when the heart failure is secondary to rheumatic myocarditis. The cardiac glycosides have barely any effect on insufficiencies caused by diphtheria toxin or hyperthyroidism. Peripheral or centrally induced circulatory failure is not an indication for treatment with glycosides. The success of treatment is also dependent on whether insufficiency is accompanied by tachycardia or bradycardia. Since cardiac glycosides also produce a positive inotropic effect on compensated, nonfailing heart muscle, these drugs may be employed prophylactically if a particular stress has to be imposed upon the heart. This is especially the case during surgical operations with a cardiac risk.

A very rare indication for glycoside therapy is auricular fibrillation or flutter in the absence of myocardial insufficiency. In that case an inhibition of membrane function, not a positive inotropic effect, is desired. If all other treatment has failed, the acute administration of relatively high doses of glycoside may be attempted.

Fate in the Organism

There are great differences in the enteral absorption of the various cardiac glycosides after oral administration. The extent of absorption varies from patient to patient. Therefore, the exact dosage is uncertain with all glycosides that are not completely absorbed. The mean values below are given as rough approximations for gross orientation. From a single oral dose approximately the following percentage is absorbed: pure digitoxin, nearly 100%; digitoxin from galenic preparations of digitalis leaves, only about 20%; native *Digitalis lanata* glycosides, 50–60%, digoxin, 50–80%, β-acetyldigoxin 60–80%, proscillaridin, 20–40%; Lanatoside C, 20–40%; and strophanthin, about 2%.

The onset of action and the time it takes for the effect to decline are equally variable for different glycosides. A summary of the most important data for therapy is given in Table III for equieffective doses.

As can be seen from the rate at which activity is lost, the accumulation of glycosides is rather variable. It is quite significant for digitoxin and practically nonexistent for strophanthin. The blood levels of ouabain and digitoxin after a single dose are shown in Fig. 26. The values were obtained in patients by means of radioactively labeled (^{3}H) glycosides.

The curves exhibit two components: (1) a rapid decline in blood level after i.v. injection representing tissue distribution and the beginning of excretion, and (2)

TABLE III

Maximal Duration of Action and Rate of Elimination of Various Glycosides (Approximate Values which Vary Markedly from Individual to Individual)

Glycoside	Route	Onset of effect (minutes)	Maximal duration (hours)	Loss of activity per day (%)
Digitoxin	per os	—	12	10
Digitoxin	i.v.	30–60	8	10
Digoxin	per os	—	6	~30
Digoxin	i.v.	5–20	3	~30
g- or k-Strophanthin	i.v.	3–10	1	~90

a slow phase which is determined exclusively by the rate of elimination. While ouabain and digitoxin can hardly be differentiated from each other during the rapid component, their different behavior during the elimination phase is apparent. Since the kidney is the main organ for the excretion of cardiac glycosides and their metabolites, renal insufficiency results in retarded elimination and thus a higher plasma level (Fig. 27). This phenomenon explains the well-known "poor tolerance" to cardiac glycosides of patients suffering from renal insufficiency. A discrepancy between the rate of elimination of the cardiac glycosides (and their metabolites) and the clinically observed loss of the therapeutic effect is frequently observed. This discrepancy is caused by the fact that on the one hand the genuine disappearance of the drugs from the organism is measured, whereas on the other hand the rate at which cardiac decompensation reappears is observed. A transient compensation

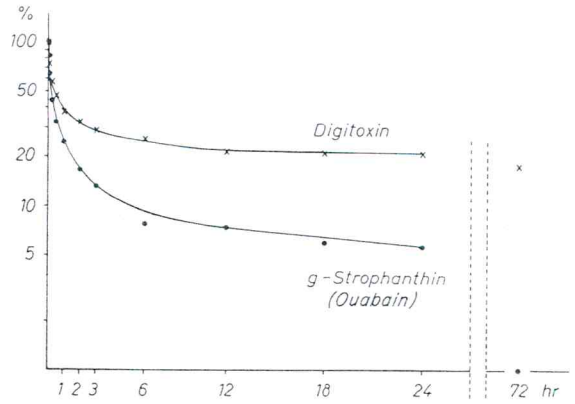


Fig. 26. Blood levels of digitoxin and strophanthin following a single intravenous dose. ^{3}H-labeled glycosides were used in order to allow for the measurement of the very small concentrations. Experiments on patients. Seventy-two hours after injection, g-strophanthin (ouabain) has completely disappeared from the blood while digitoxin and its metabolites are still easily detectable. Details in the text.

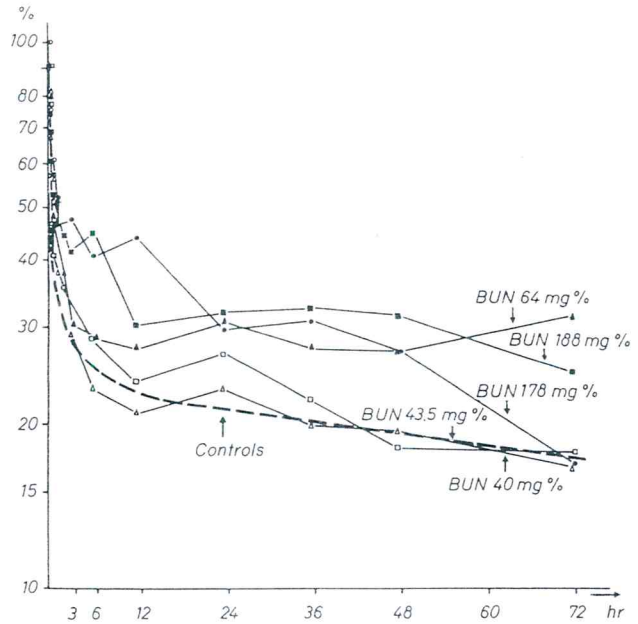


Fig. 27. Decline in serum radioactivity after an intravenous dose of digitoxin-^{3}H in control individuals (dashed line) and in patients with renal insufficiency. The serum levels of the five patients with renal disease are individually presented. As a measure of the extent of renal insufficiency, the appropriate BUN value (blood urea nitrogen) is given. Note the more prolonged excretion of the cardiac glycosides in the individuals with renal disease.

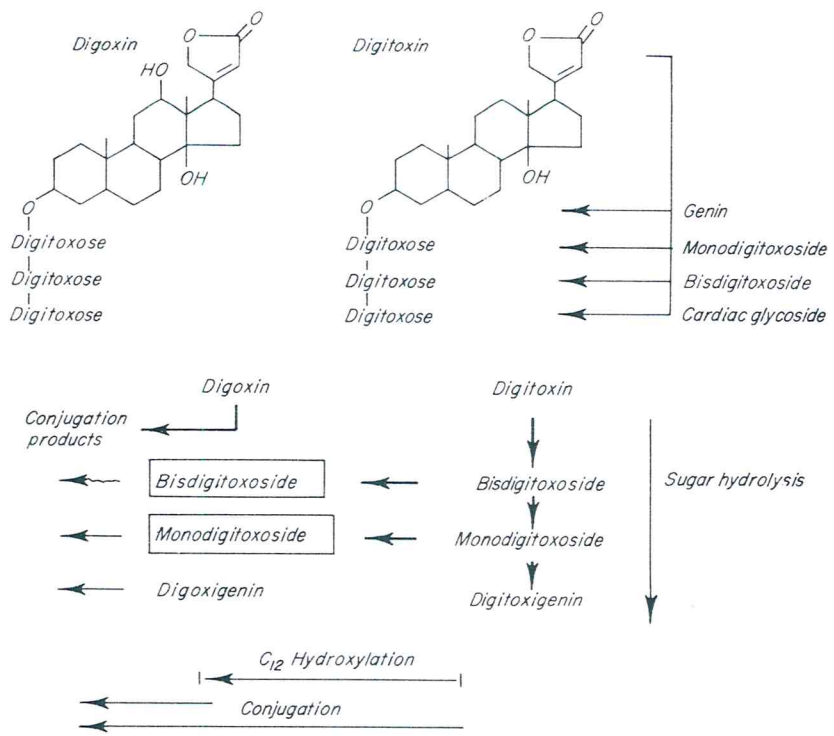
of a moderately failing heart improves the circulatory situation for a longer period of time than might be expected from the presence of the glycoside, since the cardiac edema has been excreted and the central venous pressure has decreased. Cardiac glycosides are distributed evenly throughout the whole body without specific accumulation in the heart. An equilibrium between the distribution in heart and blood is established relatively quickly. In any case, it is much more rapid than the fall in blood levels resulting from excretion. From this it follows that the duration of cardiac action is dependent solely on the rate of elimination. There is no special "affinity" of the heart muscle for the individual glycosides. In blood the glycosides are bound to albumin to some extent: digitoxin, ~95%; digoxin, ~35%, strophanthin, <5%.

The metabolic behavior of the various cardiac glycosines is rather different. In man ouabain is not changed, although chemically it is very labile as a result of the many oxygen-containing moieties. Probably, as a result of poor lipid solubility the ouabain molecule cannot penetrate into metabolically active compartments of the liver cells. It is excreted exclusively by the kidney. Digoxin loses its cardiac activity via conjugation. The conjugation products are water soluble and after their forma-

tion in the liver a portion is excreted in the bile, while the remainder diffuses back into the blood and is subsequently excreted by the kidney. The conjugation products that enter into the intestine are slowly hydrolyzed during their passage through the intestine. Part of the digoxin produced by this hydrolysis is reabsorbed from the intestine as is the unchanged digoxin that is passed from the liver into the bile. Digitoxin is subject to the most complicated metabolic degradation. As demonstrated by the schematic representation below, three different processes are competing with each other: (1) initially the removal of one or more saccharides, (2) hydroxylation at C_{12} so that the products formed belong to the digoxin instead of the digitoxin series and (3) conjugation of the metabolites. The metabolic degradation of digitoxin occurs much more rapidly than the pharmacological effect declines after administration of this glycoside. This apparent discrepancy is explained by the occurrence of cardioactive metabolites, i.e., the bis- and monodigitoxosides of digoxigenin which are rather resistant to metabolic degradation. Unchanged digitoxin cannot leave the body, since after its biliary excretion it is reabsorbed quantitatively by the intestine. Similarly after its glomerular filtration digitoxin will be liable to complete tubular reabsorption. The metabolites of digitoxin are again conjugated with acids and mainly excreted with the bile, there to be hydrolyzed and reabsorbed (enterohepatic cycle). However the conjugation products are water-soluble compounds that can leave the body via the kidneys. The long duration of action of "digitoxin" (10% loss of effect per day) is determined to a considerable degree by the occurrence of cardioactive metabolites which are relatively resistant to metabolic degradation. Furthermore, two additional factors contribute to a depotlike action: (1) Immediately after administration the hydrophobic compound digitoxin will accumulate in the various tissues. It will only slowly dissociate from lipophilic structures if the blood level decreases. (2) An important proportion of glycoside present in the body is continuously following the enterohepatic cycle and thus excretion is prevented.

Dosing of Cardiac Glycosides

The pure glycosides are preferred to any galenic preparation. The choice of drug is mainly based on the urgency with which the therapeutic effect is required. The extremes are ouabain given intravenously (maximum activity after 1 hr), and digitoxin (maximum activity after about 12 hr). The rate at which the effect declines determines the size of the maintenance dose. The lower the rate, the smaller the maintenance dose in relation to the dose which must be given at the initiation of therapy in order to achieve full digitalization. In practical use, the term, "full activity dose" (effective level), is useful, since it takes into account the daily loss of activity and the consequent necessary daily dose (see Fig. 28). For example, it lies between 1.2 and 2 mg for digitoxin, digoxin, and lanatoside, and about 0.7 mg for ouabain, squillglycoside, and convallatoxin. However, a too schematic dosing schedule is not adequate. The clinical result must always be decisive for the dosing regimen. Since the sensitivity of individual patients to glycosides varies markedly and the therapeutic index of the cardiac glycosides is rather small,



individual dosing is essential. Since only digitoxin is completely and therefore accountably absorbed and is only very slowly eliminated, it is only with this glycoside that fluctuations away from the effective level can be avoided. For this reason, digitoxin should be generally preferred. However, digoxin and β-acetyldigoxin have proved of practical value as well. Only two conditions require other glycosides: (1) In acute heart failure ouabain is called for because of its rapid onset of action. (2) After doses of digitalis which elicit centrally mediated vomiting and are below the required effective level, other glycosides should be tried. Acetyldigoxin (α or β), acetylated at one saccharide moiety possesses somewhat more hydrophobic properties than digoxin and seems to be absorbed better. With respect to its metabolic degradation and cardiac activity acetyldigoxin behaves like digoxin. This is emphasized by the fact that one firm sells under the same trade name β-acetyldigoxin in tablets and digoxin in ampules. Some initial and maintenance doses are given in Table IV.

If the cardiac glycoside is changed during a course of treatment, the typical rate at which the activity of the initial glycoside is lost and the onset of action for the second one must be considered to avoid overdosage or lapses in therapeutic effect (e.g., change from ouabain to digitoxin or vice versa).

A synergism exists between most cardiac glycosides and calcium ions; for this reason intravenous injection of calcium must be avoided in fully digitalized patients since toxic symptoms may occur.

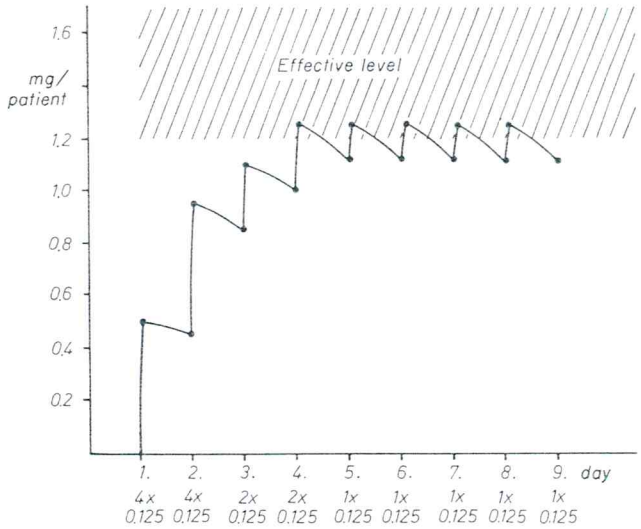


Fig. 28. Dosage regimen for digitoxin in a patient in which the effective body level is about 1.2 mg/70 kg. A loss of activity of 10% per day is assumed. Digitoxin is administered in tablets of 0.125 mg. Although the initial dose is four times higher than the maintenance dose, the necessary level of activity is only achieved on the fourth day. In the event that the patient required a higher level of activity (2.0 mg is possible), such a level would never be reached with this dosage regimen. For such a patient, this dosage schedule represents simply too low a dose.

Inactive Contaminants of Cardiac Glycosides

Galenic preparations of cardiac glycosides contain compounds without any therapeutic effect. These are saponins such as digitonin. They are very strong surface-active agents (tissue irritation and hemolysis) and do not possess any therapeutic activity. Their presence in galenic preparations decisively hinders the absorption of digitoxin. In addition, the irritation of mucosal membranes results in an inability to tolerate such preparations. For these reasons the prescription of cardiac glycosides in such forms is obsolete today.

TABLE IV

Initial and Maintenance Doses of Some Glycosides

Cardiac glycoside	Initial dose (mg/day)		Maintenance dose, oral (mg/day)
	Oral	i.v.	
Digitoxin	0.5–1.2	0.75–1.2	0.1–0.2
Digoxin	1.0–3.0	0.75–1.2	0.25–0.75
Lanatoside C	4.0–6.0	1.0–1.5	0.75–1.0
Proscillaridin	1.0–2.0	–	0.5–1.0
g- or k-Strophanthin	–	(0.25)–0.5	–

Calcium

In experimental animals it can be shown that the contractility of the heart is directly dependent on the extracellular concentration of calcium ions (Fig. 35). Increased Ca^{2+} concentrations increase contractile force while lowered concentrations have a negative inotropic effect.

The changes in extracellular calcium concentration lead to parallel changes in the intracellular calcium content. There is a relationship between the actions of calcium and those of the cardiac glycosides. The potency of other compounds with cardiac activity (epinephrine and potassium ions) is equally dependent on the calcium concentration. Therapeutically, the positive effect of calcium on the force of contraction cannot be utilized since other factors in cardiac function are also affected (stimulus formation and impulse conduction) (Fig. 34).

Catecholamines

The effect of epinephrine and norepinephrine on the circulation is complicated and is described elsewhere (cf. p. 19). The heart itself is influenced in a very complex manner. Apart from the positive chronotropic, dromotropic, and bathmotropic effects, as well as the increase in oxygen consumption and coronary dilation, the catecholamines have a marked positive inotropic effect. They elevate the permeability of the cell membrane to calcium during the duration of the action potential. Consequently, the intracellular calcium ion concentration is transiently increased to a greater extent than under control circumstances. Accordingly, catecholamines produce maximal activation of the contractile system. The receptors, which are stimulated to produce the increase in contractile force, belong to the β-adrenergic

type. The positive inotropic effect of epinephrine and norepinephrine cannot be isolated from their other effects and consequently they have no particular therapeutic importance.

Purine Derivatives

Theophylline and, to a lesser extent, caffeine increase the force of contraction of cardiac muscle. This effect is not very pronounced and hardly can be utilized for therapeutic purposes. However, the positive inotropic effect is considered a favorable "side effect" when purines are given for other indications (cf. p. 77).

Glucagon

This polypeptide (cf. p. 223) produces a modest positive inotropic effect that may be useful in occasional digitalis-resistant cases. It scarcely affects the frequency and excitability of the myocardium. Glucagon has to be administered as a long-term infusion. The mechanism of action has not been elucidated yet.

Antifibrillatory Drugs

This group of drugs contains compounds which more or less specifically depress the excitability of the heart. Such drugs are useful in the treatment of cardiac conditions resulting from hyperexcitability, like auricular flutter or fibrillation and paroxysmal tachycardia; they are sometimes used prophylactically in heart surgery that may induce arrhythmias or ventricular fibrillation.

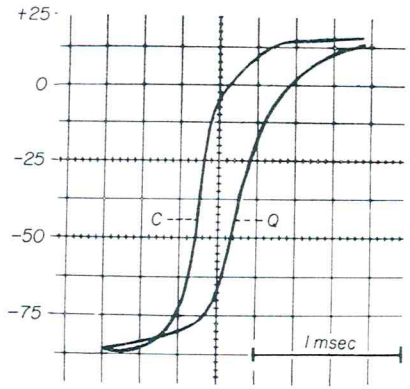


Fig. 29. The effect of quinidine on the depolarization velocity. Experiment on the isolated guinea pig atrium. The action potentials have been recorded from a single cell with intracellular microelectrodes. Only the depolarization phase is shown. Note the rapid velocity with which the oscilloscope trace is deflected (compare to the time signals). The phase of depolarization before (C) and after (Q) addition of 2×10^{-5} gm/ml of quinidine. Quinidine diminishes the rate of depolarization.

Mechanism of Action

The excitability and the conduction velocity are governed by the properties of the muscle cell membrane. Thus the refractory period is a function of the duration of the action potential, while the velocity of impulse conduction is a function of the rate of depolarization of the action potential.

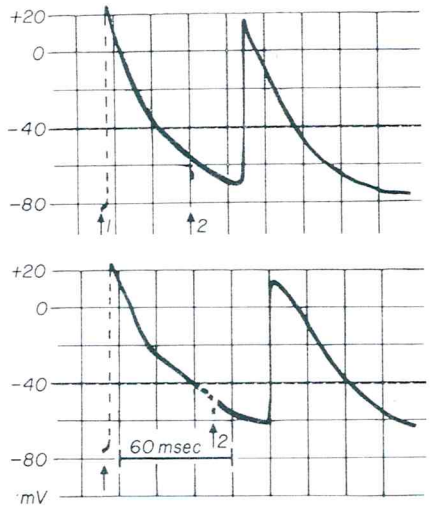


Fig. 30. The effect of quinidine on the action potential of the isolated atrium of the rat. The potential had been recorded by means of intracellular microelectrodes from single cells. The action potentials have been elicited with brief square wave stimuli. The first arrow designates the first stimulus in a regular train of stimuli with a frequency of 1 Hz; the second arrow shows the presentation of an extrasystolic stimulus. In this experiment the time interval between the regular and extrasystolic stimuli was so chosen that a propagated response to the extrasystolic stimulus was just possible—the end of the refractory period. Above: The width of the action potential and duration of the refractory period under control conditions. Below: In the presence of quinidine 10^{-5} gm/ml. Note the widening of the action potential and thereby the refractory period.

Antifibrillatory compounds decrease the rate of depolarization (slowing the increase in sodium conductance) and, thus, the velocity of impulse conduction. Figure 29 shows an experiment in which the decrease in the rate of rise of a single-cell action potential is measured by means of intracellular microelectrodes. Figure 30 demonstrates the increase in the duration of the repolarization phase and, thus, the refractory period. This effect is also caused by an affect on the ion permeability of the membrane.

Quinidine

Quinidine is an alkaloid obtained from cinchona bark and is stereoisomeric with quinine. Its influence on the heart is "negative" in all respects: decrease in excitability, decreased conduction velocity, prolonged refractory period, and lower

amplitude of contraction. It should therefore not be overlooked that quinidine causes unspecific damage to the heart. For this reason in the therapy of hyperexcitability with quinidine the rule should be: The myocardium must be sufficient, i.e., nonfailing.

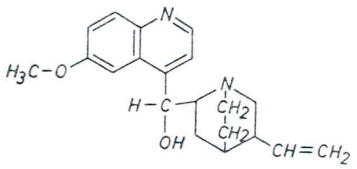
Since quinidine as well as quinine may give rise to allergic reactions, it is recommended that treatment be started with a small test dose of 0.2 gm orally. The daily dose should not exceed 2.0 gm orally. Therapy should be discontinued if no improvement is noted within 4–5 days. If therapy is successful, a maintenance dose of 0.2 gm two to four times a day may be given.

Ajmalin

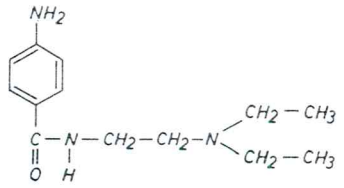
Ajmalin is found along with the main alkaloid, reserpine, in the *Rauwolfia* root. The action of ajmalin on the heart corresponds closely to that of quinidine: decreased excitability and a negative inotropic effect. The requirement is, as for quinidine, the compensation of any cardiac insufficiency before any antifibrillatory treatment is started. Present knowledge does not indicate any advantages of ajmalin over quinidine.

Local Anesthetics

Local anesthetics have an inhibitory effect on cardiac function (cf. side effects of local anesthetics, p. 134). Procaine amide, a derivative of *p*-aminobenzoic acid, has the following advantages over the related ester, procaine: It is degraded only very slowly, the action correspondingly lasts much longer, and the local anesthetic and central stimulatory effects are attenuated. It inhibits cardiac excitability and lowers the velocity at which stimuli are transmitted.



Quinidine



Procainamide
p-Amino-N-(2-diethylaminoethyl)
benzamide

If equipotent antifibrillatory doses of procaine amide and quinidine are compared, the former has a smaller negative inotropic effect. Nevertheless, myocardial sufficiency is a prerequisite for treatment with procaine amide.

Procaine amide may precipitate hypersensitivity reactions as does procaine. A test dose of the drug is recommended. Oral administration leads to irritation of the gastrointestinal mucosa (nausea, vomiting, and diarrhea). Long-continued administration can sometimes provoke symptoms which resemble those of acute lupus erythematosus.

Treatment may be started by intramuscular injection of 0.5–1.0 gm or, in urgent cases, by an intravenous infusion of 0.025–0.05 gm/min to a total dose of 0.3–0.5 gm. In order to be able to immediately combat a marked inhibition of cardiac function, epinephrine should be readily available as an antagonist. The oral maintenance dose of procaine amide is 0.5–1.0 gm four to six times a day.

Lidocaine, another local anesthetic, can be used in a similar manner as an antifibrillatory agent. The danger of hypotension appears to be less with this substance than with procaine amide. Long-acting local anesthetic agents have the advantage of a more gradual effect, but in higher dosage they may provoke centrally induced convulsions.

Diphenylhydantoin

As discussed in relation to the therapy of cardiac glycoside intoxication, this hydantoin derivative (see formula, p. 185) possesses antiarrhythmic activity. The mechanism of action appears to differ from that of the previously mentioned drugs. The depolarization phase is less affected than the resting potential. Diphenylhydantoin elevates the membrane potential, particularly when it has fallen and accordingly become unstable. It appears to be useful not only in cardiac glycoside intoxication but also in other types of ventricular extrasystoles (concerning the dosage schedule, see p. 64).

β-Receptor Blocking Agents

Many compounds in this group which have been investigated up until now possess besides their sympatholytic action, "quinidinelike" and local anesthetic effects. The ratio of these two properties varies from compound to compound. It has been shown for many compounds of this group that the sympatholytic activity is found only in the *l*-isomer, while the quinidinelike effects are found with both optical isomers. Certain therapeutic responses with the β-blockers including those obtained in the treatment of cardiac irregularities that are not induced by catecholamines may be attributed to the quinidinelike properties (cf. p. 35).

Antianginal Drugs

The purpose of the coronary circulation is to provide an adequate supply of nutrients and oxygen to the heart muscle and to remove metabolic products. The term coronary insufficiency is used to describe a gap between cardiac work and myocardial oxygen consumption. Such a condition may be caused by a variety of factors: (1) insufficient coronary flow resulting from arteriosclerosis, aberrant autonomic control, hypotension, as well as a circumscribed local anoxia with myocardial infarction; (2) by a decreased oxygen-carrying capacity of the blood as in anemia or methemoglobinemia; or (3) by increased cardiac work with a corresponding increase in the oxygen requirement. Such an absolute or relative lack of oxygen in the heart muscle, which is usually painful, is then described by

the general term coronary insufficiency. The obvious objective in the treatment of coronary insufficiency (or angina pectoris) is the improvement of the coronary circulation. However, since in this condition the coronary arteries are usually already maximally dilated, no increase in the coronary flow per unit time can be expected from drugs which act solely as coronary vasodilators. Therefore, the therapeutic goal must be to lower the cardiac oxygen requirement; that is, to diminish cardiac work. Angina pectoris in the hyperthyroid patient can possibly be improved by the administration of antithyroid drugs. A slight decrease in blood pressure lowers cardiac work substantially without diminishing passive coronary flow. It is possible that only those drugs are effective which can be so precisely dosed that the heart is relieved of some of its load by the slight fall in blood pressure.

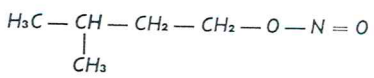
A depression of the cardiac frequency and improvement in cardiac dynamics also produces a diminished oxygen uptake by the myocardium via a reduction of the end diastolic pressure. The demonstration of a coronary dilating effect in experimental animals and in patients with normal cardiac function is without relevant importance for therapeutic efficacy in angina pectoris.

Nitrites

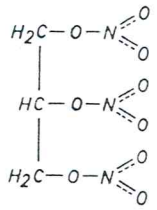
The term nitrites is not correct since collectively these compounds are inorganic nitrites, esters of nitrous acid and nitric acid.

The most important ester of nitric acid is glycerol trinitrate (nitroglycerine). The latter name is also incorrect, since nitro groups are directly bound to carbon ($R—CH_2—NO_2$).

Homologous with the structure of glyceryl trinitrate are esters of the tetravalent alcohol erythritol and of the hexavalent alcohol mannitol such as erythrytol tetranitrate and mannitol hexanitrate. The "nitrites" are vasodilators as a result of a direct affect on smooth muscles. The coronary vessels and the dermal vessels of the head and neck are particularly sensitive. Other areas respond to higher doses, leading to a lowering of blood pressure. In subjects without heart disease coronary flow is increased as long as the blood pressure remains fairly stable (recall the passive dependence of coronary circulation on blood pressure). Diminished cardiac work, with consequent depression of oxygen consumption, probably is the deciding factor in successful therapy of angina pectoris. The tonus of smooth muscles in other organs such as that of the bronchial muscles is also lowered by "nitrites."



Nitric acid ester of amylalcohol, Amylnitrite; 1–4 drops for inhalation



Glyceryltrinitrate Nitroglycerine

0.2–1.0 mg perlingual

The effective dose and the onset of action vary considerably with different compounds. Glycerol trinitrate is the only really reliable drug of this group when administered

perlingually. The so-called "long-lasting nitrites" should also be given perlingually, but even then their effect seems uncertain. The "nitrites" should be administered in such dosage that the occurrence of headache is just avoided.

Nothing is known of the actual mechanism of action of the "nitrites." It is not yet even clear if the drugs as such or their metabolites are active.

The side effects of "nitrites" in normal doses are caused by their main action: fall in blood pressure with headaches (rarely fainting) and reflex tachycardia. Intraocular pressure can sometimes be increased, and therefore caution is recommended in cases with preexisting glaucoma. The "nitrites" form methemoglobin, but this effect can be neglected with therapeutic doses. Tolerance rarely occurs.

Papaverine

This opium alkaloid which acts directly on smooth muscle is described in detail elsewhere (p. 43). It sometimes has a beneficial effect in particular cases of angina pectoris (slow intravenous dosage of 10–100 mg). Since the vascular dilation is not restricted to the coronary bed, a fall in systemic blood pressure must be expected. A quinidinelike effect is observed with higher doses of papaverine which may contribute to the favorable effect.

Quinidinelike Substances

Quinidine itself and drugs with predominantly quinidinelike properties (like iproveratril) and β-adrenergic blocking agents decrease contractile amplitude and frequency of the heart and consequently lower the blood pressure. At adequate dosage they can optimize the relationship between cardiac work and oxygen consumption. One should consider that the effect takes place by inducing a functional deficiency in the myocardium.

Purine Derivatives

Theophylline, and probably to a lesser extent caffeine, act as vasodilators, an effect also seen in coronary vessels. Since they have a multiplicity of effects (central nervous stimulation, positive inotropic effect, and alteration of the cardiac frequency), the actual mechanism that is responsible for their possibly favorable influence on coronary insufficiency is very difficult to isolate. Apart from oral treatment (200–400 mg of theophylline several times daily), slow intravenous administration (200–400 mg) is called for only under acute circumstances. As a result of the poor solubility of theophylline, a solubilizing agent is included in commercial ampules.

Dipyridamole

Dipyridamole has a demonstrable coronary-dilating effect in animal experiments and in humans. The effect results from an elevation of the extracellular concentration of adenosine that is formed intracellularly during anoxia and diffuses out of the cell to cause vasodilatation. Moderate doses of dipyridamole do not affect blood

pressure but higher doses lower it. The drug appears to have a direct metabolic effect apart from its vascular action. The heart removes relatively less oxygen from the circulating coronary blood. This effect is of no importance for the function of the heart with coronary insufficiency. In spite of the vasodilator effect of the drug in angina pectoris, well-controlled clinical trials with large groups of patients have been disappointing.

Lidoflazine

Lidoflazine enhances the effect of adenosine. Upon prolonged administration it seems to diminish the frequency at which angina pectoris attacks occur. Lidoflazine is contraindicated in myocardial infarction and in disturbances of impulse generation and conduction.

Therapy of Myocardial Infarction

The spectrum of therapeutic measures can be differently constituted depending on the pathogenesis and intensity of the infarction and the individual situation. Therefore, a simple regimen of treatment which can be employed in all cases cannot be given. However, some therapeutic principles may be enumerated at this point.

1. Maximal protection of the heart by (a) heavy sedation of the patient with the resultant loss of superfluous motor activity with corresponding demands on the circulation, (b) dissociation of psychic influences on cardiac function by "psychoautonomic uncoupling" drugs, and (c) alleviation of pain by opiates. The following drugs are indicated: phenobarbital for heavy sedation, diazepam in high doses for the "uncoupling" of cardiac function from psychic influences (chlorpromazine and closely related compounds are not suitable because the tachycardia induced by these drugs can be detrimental) and meperidine as an analgesic.
2. With myocardial insufficiency, ouabain several times in doses of 0.125 mg intravenously.
3. Against developing or existant pulmonary edema, besides general clinical management (suction, venesection being doubtful) osmotherapy is necessary with mannitol solutions or low molecular weight dextran. In addition, this improves the microcirculation. Full and rapid digitalization is also required.
4. If an arrythmia is present, one must differentiate between: (a) sinus tachycardia, probably mediated by epinephrine, which can usually be suppressed with β-receptor blocking agents. Compounds should be chosen which possess the least possible quinidinelike activity (see p. 35). (b) Arrythmias originating in the AV node can often be favorably influenced with β-receptor stimulating drugs such as isoproterenol or orciprenaline. (c) With ventricular arrythmias which have a less favorable prognosis, attempts have been made with antifibrillatory drugs (such as procainamide) and successfully with local anesthetics (lidocaine). On the basis of its different mechanism of action, diphenylhydantoin would appear to be useful (up to 0.25 gm as a continuous infusion, with a subsequent oral dose of about 0.2 gm per day).

5. Cardiac shock resulting from a myocardial infarction exhibits the following characteristics: very small pulse pressure, diminished stroke volume, elevated peripheral resistance, a marked rise in central venous pressure as the result of peripheral acidosis, and finally, irreversible damage. Regardless of whether the blood pressure is low, it is usually wrong to attempt to normalize it with pressor agents such as epinephrine or angiotensin. The "circulation-dependent" situation of the heart may be rendered worse (further increases in central venous pressure with corresponding atrial distention). True peripheral vasodilatation and an increase of the circulatory volume (with control of the central venous pressure) is required. Vasodilatation can be elicited with β-receptor-stimulating drugs such as isoproterenol or orciprenaline. If as a result of the vasodilatation, the precardiac venous pressure drops, the heart frequency also falls. This effect is more marked than the β-stimulant's intrinsic positive chronotropic effect. As a result of β-stimulation, the "circulation-dependent" situation of the heart is considerably improved (decreases in peripheral resistance, central venous pressure, atrial distention and rate). A volume deficiency develops because of the vasodilatation which is best remedied with low-molecular weight dextran. The systolic pressure need not be brought to a "normal value," but can be allowed to remain somewhat lower. In this connection two contradictory aspects are determinant. The blood pressure should be high enough to ensure an adequate supply to all organs, but as low as possible in order to protect the heart. In order to accelerate the mobilization of the interstitial edema which develops during the period of high venous pressure, rapid acting saluretics (furosemide) may be given with caution. There is a self-evident need for control of electrolyte and acid-base balance by the appropriate therapeutic measures. For the prophylaxis of reinfarction with anticoagulant agents cf. page 89. The possibility of fibrinolytic therapy in the first hours following the infraction can only be mentioned here.

The Treatment of Angina Pectoris

One should distinguish between the therapy of an acute attack of angina pectoris and the chronic treatment for reducing the frequency or intensity of attacks. The acute attack requires a rapid alleviation of pain (1) by decreasing the hemodynamic work load of the heart with nitroglycerine, administered perlingually, and (2) by analgesic-sedative treatment with opiates and psychopharmacological agents dependent on the severity of the case. The latter drugs, by sedating the patient, additionally reduce his oxygen consumption and thereby reduce the demands on the myocardium. For treatment of chronic cases in which the aim should be a long term relief of the heart from its work load, nitroglycerine may often be indispensable. In addition, drugs with a quinidinelike action (cf. p. 77) and β-adrenergic blocking agents in order to eliminate influences of the sympathetic nervous system (stressful situations) are especially suitable. Treatment with tranquilizers may be useful in reducing stressful situations. Judgment of the pharmacological effectiveness of chronic therapy is difficult since placebos may produce a therapeutic result in up to 50% of those so treated. Cardiac glycosides are called for if myocardial insufficiency is simultaneously occurring.

Blood

Anemia

Iron-Deficiency Anemia

Iron Metabolism

The healthy human being contains approximately 4.0–5.0 gm of iron, of which one-half is bound in hemoglobin. Iron is a constituent of vital enzymes such as the cytochromes. The daily loss of iron, under normal conditions, is very small, and the average daily requirement is estimated to be approximately 0.5–2.0 mg. Absorption from the intestinal tract is at a level just sufficient to compensate for the daily loss. In iron deficiency larger amounts are absorbed if they are available. Iron absorption is mediated by apoferritin-ferritin, a specific protein contained in the intestinal mucous membrane. Iron is absorbed as Fe^{2+} ions and subsequently oxidized in plasma. This oxidation is catalyzed by the only enzyme responsible for ferro-oxidation, i.e., the copper-containing ceruloplasmin, and the product (Fe^{3+}) is bound to the iron-binding protein (siderophilin, transferrin). An excessive amount of iron in the organism is prevented by the ferritin mechanism of "mucosal block" as long as an excess amount is not presented. If this line of protection is circumvented by parenteral administration of iron, saturation of transferrin is quickly reached and toxic symptoms and siderosis occur.

Iron deficiency may be caused in two ways: 1. the loss of iron is abnormally high and cannot be replaced by that in the normal diet or 2. normal daily losses result in depletion because of faulty absorption or decreased dietary intake of iron. Hemorrhagic anemias and anemias of pregnancy are of the first type while the anemia associated with achlorhydria and that occurring in newborn infants are of the second type.

Effects of Iron Compounds

The local effects of absorption of divalent (ferrous) and trivalent (ferric) salts must be differentiated. Ferric compounds have an astringent effect, and higher concentrations have a cauterizing effect. They cannot be absorbed by the intestinal mucous membrane and are thus without importance in oral treatment of iron deficiency. Ferrous salts have a much less irritating effect locally but therapeutic doses still may often cause disturbed gastrointestinal function (dyspepsia, constipation). In accidental poisoning of children, the effect on the mucous membrane may be so severe that the resultant hemorrhagic gastroenteritis may be lethal. As long as the mucous membrane is intact, absorptive poisoning does not occur.

The effect of oral administration of iron in the presence of an iron-deficiency anemia is seen in the following responses. Starting a few days after the beginning of treatment, the number of reticulocytes and the hemoglobin content rise. While the reticulocyte count falls back to normal on continued treatment, the hemoglobin content continues to rise until the normal range has been reached. If oral treatment with iron is unsuccessful (provided the diagnosis is correct), the use of concomitant

doses of acid to increase absorption can be attempted. If this is also unsuccessful, parenteral administration of iron may be considered.

Parenteral therapy which currently employs complexes of trivalent iron results in difficulties due to the low iron-binding capacity of plasma. Only 3–4 mg of iron per liter of plasma can be physiologically bound. This corresponds to about 20 mg per adult. All parenterally administered iron that cannot be converted into this bound form in plasma has a toxic effect and is for all practical purposes lost to the organism (hemosiderosis). Since about 8 mg of iron are required to form 1.6 gm of hemoglobin, (corresponding to 10% of the normal hemoglobin content per 100 ml of blood), the necessary quantity of iron (about 0.3 gm of iron per adult) requires about ten well-spaced injections.

After the parenteral administration of ferric compounds, the following acute toxic symptoms may occur: headache, nausea, vomiting, cardiac pain, and possibly collapse. Vascular walls are damaged by intravenous injections; the possibility of thrombophlebitis and thrombosis should be taken into account. As is evident from the above considerations, parenteral iron therapy should be restricted to very special circumstances and the dosage regimen of simultaneous oral iron therapy carefully considered.

Choice of Iron Preparation

A large number of ferrous compounds may be used in oral treatment, such as ferrous sulfate or ferrous chloride (0.1–0.3 gm several times daily). The lactate, gluconate, and tartrate are equally useful. Reduced (Quevenne's) iron is now obsolete. Of value are ferrous compounds in which their readily occurring oxidation to the ferric compound has been prevented by the addition of ascorbic acid.

For intravenous injection in severe cases of iron deficiency, a complex ferric compound (sodium–iron complex of α,γ-dihydroxy-β,β-dimethylbutyric acid) is available; the maximal quantity of this compound that can be given in one injection contains 20 mg of iron. The use of an iron–dextran complex for intramuscular injection seems rather dangerous since it has been demonstrated that in some species sarcomas may develop at the injection site. It should therefore not be utilized. Other organic iron compounds such as the ferri-sorbital-citrate complex do not elicit neoplasms under the same conditions.

Convincing improvement of iron therapy by the addition of cobalt or arsenic has not been demonstrated in humans. Cobalt can even result in polycythemia by stimulation of erythropoietin formation. It may have a beneficial effect in rare anemias that are resistant to iron, but there is no therapeutic indication for arsenic.

Pernicious Anemia

Pernicious anemia is also a deficiency disease resulting from the lack of a dietary factor (extrinsic factor) which is necessary for the maturation of erythroblasts. This compound has been identified as vitamin B_{12} or cyanocobalamin. The presence of a gastric factor (intrinsic factor) which is formed and secreted in the mucous membrane of the fundus ventriculi is essential for the absorption of cyanocobalamin. It is a mucoprotein consisting of galactose, hexosamine, and 13 different

amino acids. The primary defect in pernicious anemia is degeneration of the gastric mucous membrane (histamine-resistant achylia) with loss of the ability to produce intrinsic factor. Moreover, antibodies against intrinsic factor may be formed as well. Consequently, vitamin B_{12} can no longer be absorbed. The structure of cyanocobalamin is known, the empirical formula being $C_{63}H_{90}CoN_{14}O_{11}P$ (molecular weight, 1356). The special feature of this compound is the presence of a single cobalt atom which is bound as a chelate to nitrogen atoms with one primary and four secondary valences, while the other primary valence is linked to the cyanide moiety. The latter group is not essential for activity. It can be replaced by a hydroxyl group, the compound then being called hydroxocobalamin, which has the same qualitative activity as cyanocobalamin. However, it is more slowly excreted and therefore has a more potent, and prolonged action than cyanocobalamine. Vitamin B_{12} is synthesized exclusively by microorganisms, and cultures of *Streptomyces griseus* are used in commercial production. Mammalian liver is a rich source of cyanocobalamin (0.5 mg/kg). The high content in liver explains the first successful treatment of pernicious anemia with very large amounts of liver (up to 500 gm/day), and the activity of liver extracts given parenterally. Those treatments are now obsolete.

The daily requirement of an adult is about 1–2 μg of cyanocobalamin. It is absorbed from the lower ileum. Cyanocobalamin produced by microorganisms in the large intestine is not absorbed by the body and is lost with the feces. The total content of B_{12} in a human is about 2 mg, a considerable quantity. Since the daily urinary excretion is very low (less than 0.3 μg), the effects of insufficient intake become noticeable only after a long time.

A patient with pernicious anemia has a much lower content of cyanocobalamin in the blood and tissues; treatment therefore should be started with high parenteral doses (0.05–0.2 mg intramuscularly for several days) to replenish the depots. Thereafter a maintenance dose of 2 μg/day (15 μg/week or 60 μg/month) is sufficient. Because side effects, even allergic reactions, are not known, the administration of excessive doses poses little risk.

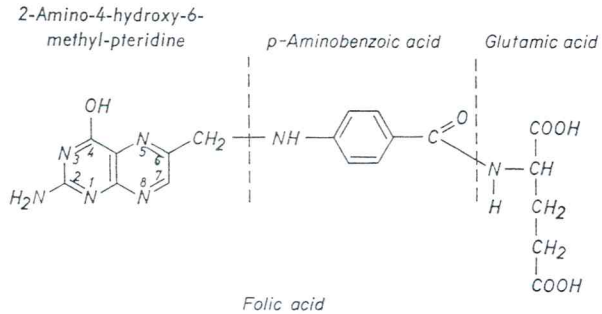
Oral administration of cyanocobalamin is not sensible in pernicious anemia, since it is faulty absorption that brings about the disease in the first place. A very high dose by mouth (about 200 μg/day instead of the usual maintenance dose of 2 μg), may result in a slight absorption, the extent of which remains, however, uncertain. A combination of intrinsic factor and moderate doses of B_{12} has not been as satisfactory as parenteral administration. The improvement in absorption resulting from a preparation of hog stomach decreases during the course of therapy.

The effect of cyanocobalamin on pernicious anemia is seen in the normalization of the formed elements of the blood (the first sign is reticulocytosis). The maturation of erythroblasts in the bone marrow begins again while megaloblasts disappear. Disturbances in intestinal function and atrophic inflammation of the mucous membrane of the tongue show improvement. Atrophy of the mucous membrane of the stomach and the histamine-resistant achylia persist. Disturbances in the central nervous system regress, unless they are too far advanced, but such regression takes a long time. Patients show such a high level of overall improvement

that one can speak of a symptomatic cure. However, since the initial condition, lack of intrinsic factor, is not cured, therapy with cyanocobalamin must always be continued. On the basis of experiments with microorganisms (e.g., *Lactobacillus lactis*), B_{12} must be a growth factor that affects the synthesis of nucleic acid precursors. Among other things, it activates the formation of succinyl CoA from methylmalonyl CoA. It is presently unclear why the hematopoietic system and the nervous system are particularly affected by vitamin B_{12} deficiency.

Cyanocobalamin-Resistant, Macrocytic Anemia

Apart from pernicious anemia, there are anemias characterized by abnormally large erythrocytes, which do not involve atrophy of the mucosal lining of the stomach (no lack of intrinsic factor) and in which B_{12} possesses no therapeutic effect. These diseases include megaloblastic anemias of children and pregnant women and disturbances in hematopoiesis, following sprue and nutritional deficiencies. Further, megaloblastic anemias are observed as side reactions to certain



Folic acid

drugs (e.g., antiepileptics and in rare cases after oral contraceptives). Common to these macrocytic anemias is the beneficial effect of folic acid.

In folinic acid the N in the 5-position is substituted with a formyl group $-C\overset{O}{\underset{H}{<}}$ while the pteridine ring is partially reduced (no double bonds in positions 5–6 and 7–8). This compound acts as an "active formaldehyde" for the transfer of one-carbon fragments and is in this way of importance in the synthesis of nucleic acids.

Folic acid is widely distributed in plant leaves. It is well absorbed from the intestine and in part transformed by the body into the actual biologically active form, folinic acid. The daily requirement in healthy adults appears to be below 1 mg. A folic acid deficiency is characterized by inhibition of cytosis, especially in the erythrocytic series. Leukopenia also may occur. Folic acid deficiency is ex-

tremely rare but may be imitated by specific antagonists such as aminopterin, a cytostatic compound (cf. "antimetabolites," p. 306).

The macrocytic forms of anemia described above are improved by oral doses of 10–20 mg of folic acid per day per adult. The hematological findings in pernicious anemia are also favorably affected, but not the other symptoms. It is therefore wrong to treat pernicious anemia with folic acid. It is also dangerous to continuously supply folic acid with polyvitamin preparations since the appearance of pernicious anemia is not only hidden but may even be enhanced because folic acid diminishes the vitamin B_{12} content of the blood.

Aplastic and Hemolytic Anemia

Both the aplastic and hemolytic forms of anemia can have very different causes. They appear as side reactions to drugs. Specific therapy does not exist, and treatment is usually restricted to the elimination of the eliciting cause or a course of symptomatic treatment. (Concerning a possible mechanism for the occurrence of hemolytic anemia as a side effect of drugs see p. 333.)

Blood Coagulation

Blood clotting is a very complex process, and pharmacological interest here is restricted to the sites of action of drugs. As can be seen from the very simplified scheme (Fig. 31), three mechanisms are available by which the clotting process may be influenced; two of these have an immediate effect while the third (inhibition of synthesis in the liver) has a comparatively long latent period.

Removal of Calcium Ions

The clotting of blood requires the presence of calcium ions at several points. Soluble, complex-bound calcium is not sufficient. In this sense blood clotting shows a certain similarity to the motor end plate and the heart. In each case the concentration of calcium ions is critical. Correspondingly, blood clotting may be suppressed by any reaction that removes calcium ions. Calcium may be removed either by conversion to a complex with the sodium salt of ethylenediaminetetraacetic acid (Na-EDTA) or with sodium citrate or by precipitation with sodium oxalate. These methods of suppressing clotting, however, can only be used *in vitro*, since removal of calcium *in vivo* leads to severe tetany. In case of emergency it may be useful to infuse a patient with a limited amount of blood containing citrate. The limit of safety with citrate is an infusion of 1 mg/min per kilogram body weight.

Sodium citrate is usually added to prevent clotting of blood *in vitro*. Four volumes of blood are mixed with one volume of 3.8% sodium citrate solution, which is isotonic with blood. This process has the advantage over an addition of heparin that blood clotting can be prevented as long as required, but the process can be immediately reversed by addition of calcium ions.

Heparin

High concentrations of heparin occur, together with histamine, in mast cells, which are particularly abundant in pericapillary connective tissue. Heparin can be specifically stained in these cells by toluidine blue because it is a sulfated mucopolysaccharide. The liver, lung, and peritoneum are especially rich in heparin. Heparin is a polymer with a molecular weight of about 20,000. The smallest unit is a tetrasaccharide, esterified with sulfuric acid. The number of sulfate residues per tetrasaccharide unit does not appear to be constant; thus, the chemical structure of heparin is not completely known.

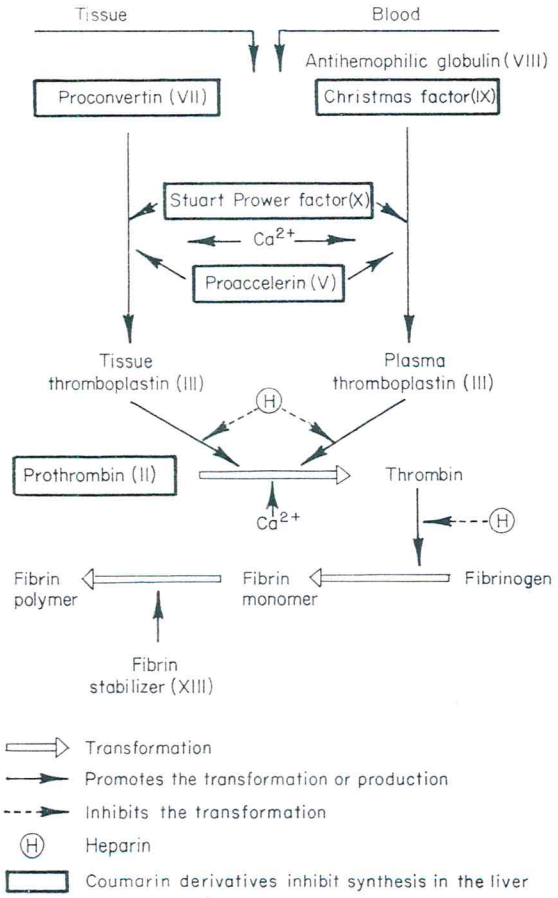
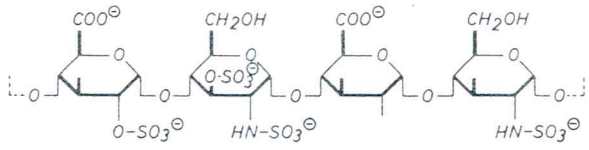


Fig. 31. Simplified, schematic representation of blood clotting and potential sites for pharmacological intervention.

Owing to the many sulfuric acid residues, heparin appears to be the strongest acid yet discovered in the mammalian organism. The strong negative charge of the molecule appears to be essential for the inhibition of coagulation by heparin; the exact mechanism is not yet known, however. Salt formation with organic cations such as protamine promptly abolishes the effect of heparin.



Heparin

Heparin may have a physiological function in the inactivation of small amounts of released thromboplastin (thrombokinase), thus preventing thromboses, although it does not hinder platelet aggregation and microembolic episodes. It does further activate fibrinolysis. From these actions, its use *in vivo* is evident as a prophylactic and therapeutic agent against thrombosis, coagulopathia and embolism. Since heparin is degraded quite rapidly in the organism, it must be readministered every few hours.

The prophylactic dose against thrombosis is usually about 50–150 mg of heparin every 2-4 hr parenterally.* In embolism an infusion may be given intraarterially (10–40 mg/hr). Heparin is added (5 mg of heparin to 100 ml of blood) to blood to be used for transfusions. The quantity is so small that it does not affect clotting in the patient receiving the transfusion. Heparin that is added to blood *in vitro* slowly loses its effectiveness under storage conditions. Fresh additions thus should be made at regular intervals. For chronic heparinization after a myocardial infarction, in order to lessen the chance of a reoccurrence, depot preparations of heparin are available which are injected daily or every second day.

Apart from its action on blood clotting, there is a clearing effect *in vivo* on lipemic blood; the basic mechanism appears to be related to an activation of lipases. Concentrations of heparin required for this effect are much lower than those used in the prevention of blood clotting. Attempts to favorably influence human arteriosclerosis by changing serum lipoproteins with heparin have not yielded convincing results. It is, however, possible to suppress all symptoms of essential xanthomatous hyperlipemia by continuous treatment.

By virtue of the elevated tendency to bleed, a number of contraindications must be watched for in the use of heparin: open wounds, uterine bleeding, gastric or intestinal ulcers, severe hypertension, central nervous system surgery, liver and kidney disease, and age beyond 70 years. If serious bleeding develops, the activity of heparin can be immediately abolished by slow injection of protamine sulfate (5 ml of a 1% solution).

The side effects of heparin particularly depend on the purity of the preparation. There is a danger of sensitization in all lots that are not highly purified. It is, therefore, not recommended that treatment be started anew after a pause of 1–2

* 1 mg of heparin contains at least 100 IU according to international pharmacological standards.

weeks. Some patients lose their hair upon treatment with heparin, but it usually grows again after 2–3 months so that only rarely does baldness persist. After months of therapy with daily doses of over 150 mg, osteoporosis can develop.

Heparinoids

This term is applied to semisynthetic polysulfate esters of saccharides that also are active in inhibiting blood clotting. All compounds investigated until now have a much lower therapeutic index than heparin, and their use in medicine can be recommended only with reservation.

Hirudin

To enable the leech to withdraw a sufficient quantity of blood from its victim through a skin wound, its glandular secretions contain a compound that reacts with thrombin, inactivates it, and thus prevents clotting. This compound, which is called hirudin, is available as an ointment; whether absorption through the skin occurs, and thus to what extent local thrombophlebitis can be affected, remains subject to debate.

Arvin

Arvin is a poison derived from the venom of a Malaysian viper, *Agistrodon rhodostoma*, which lowers the plasma level of fibrinogen faster than it can be synthesized. The action lasts for days and is independent of the coagulation and fibrinolysis systems. Clinical application to arterial and venous thromboses appears hopeful; favorable results in thrombosis of the central vein of the retina have been described.

Inhibition of Synthesis of Blood-Clotting Factors in the Liver

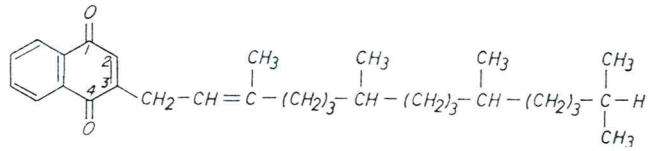
Dependence of the Synthesis on K Vitamins

Prothrombin and factors V, VII, IX, and X are synthesized in the liver. The synthesis can occur only in the presence of factors that are collectively called vitamin K. These vitamins appear to be the prosthetic group (coenzyme) of an enzyme system responsible for the formation of the specific blood proteins. The naturally occurring vitamins are called K_1 (phytonadione) and K_2. They are derivatives of naphthoquinone that have a methyl group in position 2 and a long, unsaturated side chain in position 3. They are not soluble in water and can be absorbed by the intestine only if sufficient bile is available.

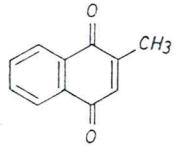
The study of simpler compounds gave the following structure-activity relationship. The active component is 2-methyl-1,4-naphthoquinone (vitamin K_3, menadione). If the methyl group is lacking, the compound has no activity; elongation of the chain in position 2 has a similar effect. Short-chain substituents in position 3 also abolish activity. Only very long chains, as in the natural K vitamins, produce an active molecule.

The daily requirement of vitamin K cannot be exactly determined, since it is not only ingested with food (vegetables and vegetable oils) but also is formed in considerable quantities by the intestinal bacterial flora.

Vitamin K deficiency can occur under the following conditions: insufficient absorption due to lack of bile (in biliary obstruction) and absence of vitamin K-synthesizing microorganisms in the intestine (frequent side effect of broad-spectrum antibiotics and as a physiological condition in the newborn until the intestine is populated).



Phytomenadione = Vitamin K_1
2-Methyl-3-phytyl-1,4-napthoquinone



Vitamin K_3, Menadione
2-Methyl-1,4-napthoquinone

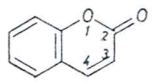
The following are indications for use of vitamin K.

1. All liver and gall bladder diseases that can result in a decreased prothrombin level because of insufficient absorption of the fat-soluble vitamin K. Water-soluble preparations are preferred for this purpose because they are easily absorbed
2. Hypoprothrombinemia of the newborn (possibly administered prophylactically prior to delivery)
3. Sterilization of the intestinal tract by broad-spectrum antibiotics with the resultant depression of vitamin K synthesis
4. All functional intestinal disorders accompanied by inhibition of fat absorption (e.g., sprue)
5. As antidotes for the coumarin derivatives (see below)

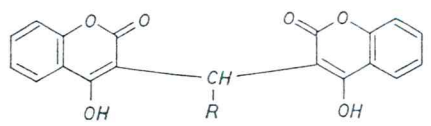
The dosage in adults is about 15–50 mg/day. Larger quantities (e.g., 200 mg vitamin K_1 parenterally) must be given to counteract an overdose of a coumarin. Very cautious administration is indicated in the newborn; a total of 1 mg given parenterally is sufficient. Larger amounts may result in serious side effects in premature and other infants. Hemolytic anemias and death from kernicterus have been reported following high doses of vitamin K preparations.

Action of Coumarin Derivatives

Coumarin and related compounds are vitamin K antagonists as a result of their affinity for the apoenzyme which has vitamin K as a coenzyme. Vitamin K and the coumarin derivatives compete for the apoenzyme (note the similarity in chemical structure). However, the coumarin–apoenzyme complex is biologically inert so that clotting factors cannot be synthesized. The inhibition is very specific as other



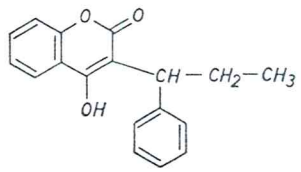
Coumarin (fragrant material from species of sweet clover and woodruff = Asperula odorata)



(1) R = H
bishydroxycoumarin, dicumarol
3,3'-Methylenebis[4-hydroxycoumarin]

(2) R = $-C(=O)-O-C_2H_5$

Ethyl biscoumacetate
3,3'-Carboxymethylenebis(4-hydroxycoumarin)ethyl ester



Phenprocoumon
3-(α-Ethylbenzyl)-4-hydroxycoumarin

liver functions are not affected. The mechanism of action of the coumarin derivatives explains why they have activity only *in vivo* and not *in vitro* as is the case for heparin or citrate. The mechanism also explains the very slow onset of action. The blood clotting factors in the circulating blood must first disappear in the course of 1–3 days by normal turnover before the failing supply from the liver is expressed as a depression in the levels of the clotting factors. The competitive nature of the reaction also explains the varying sensitivity of individuals. The more vitamin K contained in the liver, the less sensitive that organ is to the effects of coumarins and vice versa. If the administration of vitamin K antagonists is interrupted, the liver again begins to synthesize clotting factors, and blood clotting normalizes within a few days. Large amounts of vitamin K_1 (phytonadione) can counteract the effects of an overdose of coumarin derivatives, and reactivate the synthesis of clotting factors more rapidly.

Indications for coumarins are similar to those for heparin, namely, the prevention of thromboses and embolisms after surgery and the treatment of thrombotic and thrombophlebitic conditions. Prophylaxis is possible with the coumarins in a case of myocardial infarction. Prolonged prophylaxis may carry a certain risk. Its success is doubtful if the activity of the coagulation factors is not sufficiently depressed. If an immediate effect is required, therapy should be started with heparin. Simultaneously, coumarin administration is begun which becomes effective within 1–3 days, depending on the dose and the specific drug used. Treat-

ment with coumarins must not be carried out in a purely routine manner, but must be individual with control of the clotting factor levels. The so-called Quick value should be about 20–30% of normal. After sudden discontinuation of the drugs there is the danger of a rapid increase in coagulability of the blood; cessation of the therapy should therefore be carried out gradually.

Side effects stem mainly from the desired effect, namely, inhibition of blood clotting. Bleeding may occur in all visceral organs (gastrointestinal tract and urinary tract), and subcutaneous bleeding and bleeding from wounds have been observed. In contrast to heparin, coumarins pass the placental barrier. Pregnancy and lactation are contraindications, and breast feeding ceases to be dangerous only 5–8 days after discontinuation of coumarin treatment. Hypersensitivity reactions, such as diarrhea and urticaria, may occur. Another side effect may be loss of hair as in heparin therapy. Coumarins can also damage the capillaries. Petechia, multiple ecchymoses with tissue necrosis, and swelling of glomerular loops occur. It is not clear to what extent a causal relationship exists between the damage to capillary function and the lack of blood-clotting ability.

Such bleeding is nearly always caused by an overdose with too marked a fall in the prothrombin level. Such an overdose can be more quickly counteracted by the administration of large amounts of vitamin K_1 (phytonadione). Lack of prothrombin or clotting factors can be immediately overcome by means of a blood transfusion.

A large number of coumarin derivatives are commercially available for clinical use with very little difference among their essential activities. They are only differentiated by their rate of excretion, which influences the maintenance dose level and the time it takes for the effect to disappear.

The drugs below are given in the order of the most to the least rapid loss of activity (the percentages indicating the maintenance dose as a fraction of the initial dose). Ethyl biscoumacetate (~50%), acenocoumarin (~45%), bishydroxycoumarin (~ 25%), phenprocoumon (~ 15%).

The effect of coumarin derivatives was discovered during investigations of a hemorrhagic disease of cattle in Canada and the northern United States. The increased bleeding tendency was always present after the animals had ingested spoiled sweet clover. From this feed alone it was possible to isolate about 40 compounds with antivitamin K activity. The simplest molecular structure capable of inhibiting synthesis is 4-hydroxycoumarin; substitution in position 3 increases the activity. Compounds of indandione-(1,3) are also active as vitamin K antagonists. The close structural relationship to 4-hydroxycoumarin is apparent. Phenindion (2-phenylindandione), which has been used therapeutically, should not be employed because of very severe side effects which can be lethal.

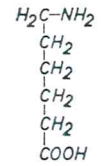
Fibrinolysis

The fibrin of fresh thrombi can be split into polypeptides and thus dissolved by means of the enzyme plasmin (fibrinolysin). Plasmin is formed from plasminogen, which is contained in the globulin fraction of the plasma.

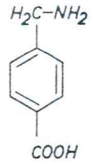
The transformation of plasminogen into plasmin is accelerated by streptokinase, which is produced by various strains of hemolytic streptococci. An intravenous

infusion of highly purified streptokinase can be used sometimes successfully in the attempt to lyse the clot immediately following its formation in thromboembolic diseases and coronary thromboses. Even after days, weeks, or months, recanalization may be observed in arterial and venous thromboses, possibly because the organized thrombi did not fill the lumen completely. If the thrombi are organized properly, plasmin and therefore also streptokinase no longer show activity, since intact cells cannot be digested. The dose of streptokinase is difficult to establish because it must depend on the quantity of circulating antibodies. Individual sensitivity can be determined by measuring the number of streptokinase units necessary to reverse coagulation in the blood from a patient within a fixed time. Rational use of streptokinase thus is tied to laboratory findings *in vitro*. The consequences of an overdose of streptokinase leading to extensive fibrinolysis can be overcome by administration of ε-aminocaproic acid or preferably *p*-aminomethylbenzoic acid, or its ring hydrated analog, *p*-aminomethylcyclohexane carboxylic acid (tranexamic acid). Fever with fits of shivering, headaches, arthralgia, nausea, and a general feeling of malaise are frequent following intravenous infusion of streptokinase. These side effects can be ameliorated by concomitant doses of glucocorticoids. Every condition that requires normal blood-clotting capacity and the presence of fibrin is a contraindication to streptokinase administration. Examples are: bleeding of various etiologies, surgery, increased inclination to bleed, and severe hypertension. The use of this plasminogen activator, streptokinase, therefore must be preceded by study of the patient's clotting status. Therapeutic experiments with urokinase obtained from human urine have up to the present given favorable results.

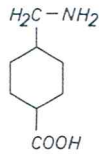
While highly purified preparations are required for intravenous injections, local application requires a less strictly pure preparation which contains in addition a second enzyme of hemolytic streptococci, i.e., streptodornase. This enzyme splits nucleoproteins into purine bases and pyrimidine nucleosides, leading to a liquefaction of purulent exudates. The nucleoproteins of pus are derived from dead cells (leukocytes and tissue cells). The combination of streptokinase and streptodornase, both incapable of harming intact cells, is used to dissolve fibrinous or purulent exudates in body cavities and necrotic wounds. These preparations must be used only locally, e.g., in the lumbar or pleural area, in joint cavities, or on surface wounds. Fresh bleeding is a contraindication, since coagulation is inhibited. The enzyme combination is also useless in newly occurring inflammations without fibrinous or pustular deposits.



ε-Aminocaproic acid



p-Aminomethylbenzoic acid
PAMBA



trans-4-(Aminomethyl) cyclohexanecarboxylic acid, AMCHA, tranexamic acid

Inhibitors of Elevated Fibrinolysis

This condition, as it occurs with streptokinase therapy, can be relieved by administration of ϵ-aminocaproic acid or tranexamic acid. In some internal diseases severe bleeding develops as the result of elevated fibrinolysis. Examples are: pneumonia, colitis, hemoblastosis, bleeding after surgery (particularly after prostatectomy as the result of the fibrinolytic activity of urokinase), and severe hemorrhage developing after childbirth. In conditions of this type coagulation may be normalized quickly upon administration of *p*-aminomethyl cyclohexane carboxylic acid or *p*-aminomethylbenzoic acid. The activity of ϵ-aminocaproic acid is weaker and of shorter duration. These compounds in turn may cause glomerular thrombosis, but also bleeding. On the other hand, the loss of menstrual blood may be reduced, since the local fibrinolytic activity is increased during this period.

Blood Substitutes

In the replacement of lost blood one has to consider whether life is menaced by lack of erythrocytes or by a functional deficiency due to lack of volume. If an acute loss of blood has caused such a serious deficiency in available erythrocytes that oxygen transport into the tissues is no longer assured and the life of the patient is in danger, fresh blood, preserved whole blood, or an erythrocyte concentrate must be given. The same treatment is also called for if a life-threatening anemia has slowly developed.

In all cases in which the danger does not result from a deficiency of erythrocytes but rather represents a disorder of the circulation resulting from an absolute or relative volume deficiency (shock), it is sufficient to infuse blood plasma or plasma substitutes instead of whole blood. Since such substitutes can be prepared and stored much more easily than blood, they are the obvious preparations for use in emergencies. When, as frequently occurs, both erythrocyte and volume deficiency exist, it is necessary to follow the infusion of a plasma substitute (which has served to bridge the acute situation) by a transfusion of whole blood several hours later.

The following requirements must be fulfilled by a plasma substitute. The colloid-osmotic pressure must be equivalent to the osmotic pressure of plasma. The colloid must be biologically inert and disappear from the body with time. In this respect it should remain in the circulation long enough to ensure a sufficiently lasting effect on the blood volume. Isotonic salt solutions, such as Ringer's or Tyrode's solution, or isotonic sodium chloride, disappear very quickly from circulation since the water is taken up into the tissues from the blood vessels because of a lack of colloid-osmotic pressure. Three preparations are now available which are based on totally different chemical compounds. Common to all compounds is an average molecular weight of 25,000–70,000. Consequently they are excreted, even though slowly, by glomerular filtration in the kidney. In the treatment of shock, the volume deficiency appears to respond better to dextran than to polyvinylpyrrolidine or gelatin derivatives.

Dextran

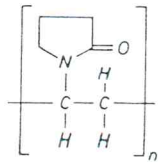
Dextran is a polysaccharide synthesized by the bacterium *Leuconostac mesenteroides*. The native product contains about 200,000 glucose molecules, mainly with 1,6-glycosidic linkages. Hydrolysis produces breakdown products with molecular weights of around 60,000. The dextran used as a plasma substitute contains 6% dextran and 0.9% sodium chloride. It is a good plasma substitute; the duration of action is 12–18 hr. It is excreted in part by the kidney (approximately 50% in 24 hr). The remainder can be degraded slowly in the body (the 1,6-glycosidic linkages, which are unusual in mammals and in man, inhibit faster degradation). Dextran has no detrimental effect on the functions of the parenchymatous organs; it occasionally possesses antigenic properties, which seem to depend on the purity of the preparation. The newer, more highly purified preparations hardly ever provoke hypersensitivity reactions (itching of the skin, urticaria, etc.).

Furthermore, a longer bleeding time accompanied by unchanged clotting time, an accelerated erythrocyte sedimentation rate, and an intravasal aggregation of erythrocytes may occur. A salt-free solution of 10% dextran is available for osmotic therapy. However, because of its slow rate of renal excretion, its osmotic effect is significantly less than that of compounds which are rapidly eliminated by the kidney (cf. p. 95). A 10% solution of low-molecular-weight dextran (molecular weight about 40,000) can be used to dissolve aggregations of thrombocytes and erythrocytes (sludge formation). This results in an improved microcirculation. However, renal damage has occasionally been observed with accumulation of dextran in the tubular epithelium after several days of infusion.

Dextran presents a good example of the fact that there are species which react to a compound unusually and unpredictably. Dextran is extremely poisonous to rats. It is used in experimental medicine to elicit reproducible local edema by injection into a rat's paw. The edema can in turn be relieved by antirheumatic agents. This single example shows how important it is to test new drugs in different animal species before investigations are carried out in humans.

Polyvinylpyrrolidone

Polyvinylpyrrolidone is a purely synthetic polymer with an average molecular weight of about 30,000. A commercial preparation contains 4% polyvinylpyrrolidone in physiological saline. It is similarly suited as dextran as a plasma substitute. It possesses no antigenic properties.



Monomer of polyvinylpyrrolidone

Three days after infusion 50–75% of the administered polyvinylpyrrolidone has been excreted. A small amount is accumulated in the reticuloendothelial system. Although the substance cannot be degraded in the body, a functional

disturbance of the reticuloendothelial system by the deposited polymer has not yet been established. Upon comparison of dextran and polyvinylpyrrolidone, it should be noted that the nonantigenicity of the latter is an advantage, but the insusceptibility to degradation in the tissues is a serious disadvantage. The physicochemical behavior of the plasma and erythrocytes is changed by both compounds similarly. It has been claimed that a polyvinylpyrrolidone of a lower average molecular weight (12,500) has the property of binding bacterial toxins and promoting their excretion. However, a convincing therapeutic effect has not been observed. The carbonyl oxygen lends the molecule certain polar properties.

Gelatin

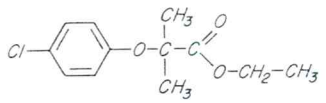
A 6% solution of gelatin in physiological sodium chloride solution can theoretically be used as a plasma substitute. Since such a solution has to be liquefied by warming to 50°C before use, and kept at this temperature during the infusion, its use has not become widespread. Recently it has become possible to thermally degrade gelatin to molecules of an average molecular weight of 12,000–15,000, which are then crosslinked by urea bridges to form a new polymer of molecular weight 35,000. A 3.5% solution remains liquid at temperatures as low as 4°C. It has no antigenic properties. Because of its high content of calcium, caution is advised with fully digitalized patients. The half-life in the circulation is given as 4 hr, very similar to that of dextran and polyvinylpyrrolidone.

Serum and Plasma Preparations

Hypovolemia can be treated by blood transfusions and by the infusion of human plasma proteins. Such procedures are not free of risk. Preparations for this purpose are available (human albumin and human plasma protein fraction). A preparation of practically unlimited shelf life is lyophilized plasma in the form of a powder that has to be redissolved prior to use. For the simple treatment of hypovolemia these preparations are usually not necessary (and too expensive). Their use is restricted to special indications, such as parenteral protein-substitution therapy, protein deficiency, etc.

Lipid Content of the Blood

All compounds that have been used up to now in the pharmacological treatment of arteriosclerosis have at best corrected only one symptom of the alterations accompanying the disease. Usually attempts were made to lower the elevated cholesterol level. This measure is based on the one-sided point of view that the cholesterol level is the most important symptom of sclerotic diseases. Actually, there is a much better correlation between ischemic heart disease and the level of neutral fat in blood, rather than that of cholesterol. Since it turned out that a cholesterol-poor diet was unsuccessful in diminishing the blood cholesterol level, inhibition of endogenous synthesis was attempted. This led to serious toxic responses. Some compounds depressed cholesterol levels, but sometimes simultaneously even increased the levels of neutral fat. Clofibrate is a compound that lowers the blood cholesterol and triglyceride levels and prolongs the time required for complete coagulation. Sustained depression of the increased lipid content of the blood can be achieved with long term therapy. So far, it is impossible to judge the consequences of this effect in terms of the development of arteriosclerosis. The effect of clofibrate requires the presence of thyroid hormone.



Clofibrate
2-(p-Chlorophenoxy)-2-methylpropionic acid ethyl ester

Kidney and Electrolytes

Kidney

Urine Production

Proximal Tubule

The glomerular filtrate, an ultrafiltrate that contains all dissolved plasma components except protein and other compounds of high molecular weight (70,000 or more), is formed in the glomerulus. On further passage through the nephron, the active transport of sodium is undertaken by tubular cells, and the sodium is reabsorbed from the tubular lumen into the peritubular interstitial space. The concomitant reabsorption of water is a passive physicochemical phenomenon caused by the osmotic gradient resulting from the sodium transfer. No energy is required for the reabsorption of water. The same holds true for the reabsorption of chloride drawn passively out of the tubular lumen by the electrochemical potential brought about by the transport of the positively charged sodium. Along the whole nephron the fluid in the lumen is electronegative with respect to the peritubular fluid. Thereby, in an unspecific manner, the reabsorption of anions into the cells and the passage of cations into the lumen is already favored. Of course, a large number of other low molecular weight compounds such as glucose, amino acids, potassium, and many others are also reabsorbed.

The Countercurrent System

After reabsorption of at least 80% of all sodium, chloride, and water in the proximal tubules, the urine still has an osmotic pressure identical to that of plasma (300 mosmoles/liter). It is then concentrated more and more as it passes through the medulla to the tip of the renal papillae (to a maximum of 1400 mosmoles/liter). This is possible because the tubular cells in the ascending limb of the medullary loop (loop of Henle) promote an active transport of sodium into the interstitial space, with chloride again following passively. Since the ascending limb is connected to the descending one via the interstitial space as well as to the vasa recta which supply Henle's loop and collecting ducts, this hairpin countercurrent system

makes it possible to maintain the same osmotic pressure in all tissue that is at the same level in the medulla. The result is a removal of sodium and chloride through the vasa recta; urine isotonic with plasma or even hypotonic appears in the distal tubule. Here and in the collecting tubules sodium is again reabsorbed (Fig. 32).

Renin and Angiotensin Mechanism

Renin liberated in the juxtaglomerular cells of the kidney influences renal blood flow by the formation of the vasoconstrictor agent, angiotensin (Fig. 32). The formation of renin or angiotensin is dependent upon the urinary sodium content or more likely on that of the resorbed fluid in the distal convoluted tubule. Injection of hypertonic sodium chloride into this part of the nephron elicits local vasoconstriction in the cells of the macula densa along the way and cessation of urine formation in *this single* nephron. This is an indication of a local influence of the macula densa on the neighboring renin-producing juxtaglomerular cells. By such a mechanism, temporary depression of urine formation, for example in shock, can lead to a prolonged cessation of blood flow in the nephron, even after the systemic

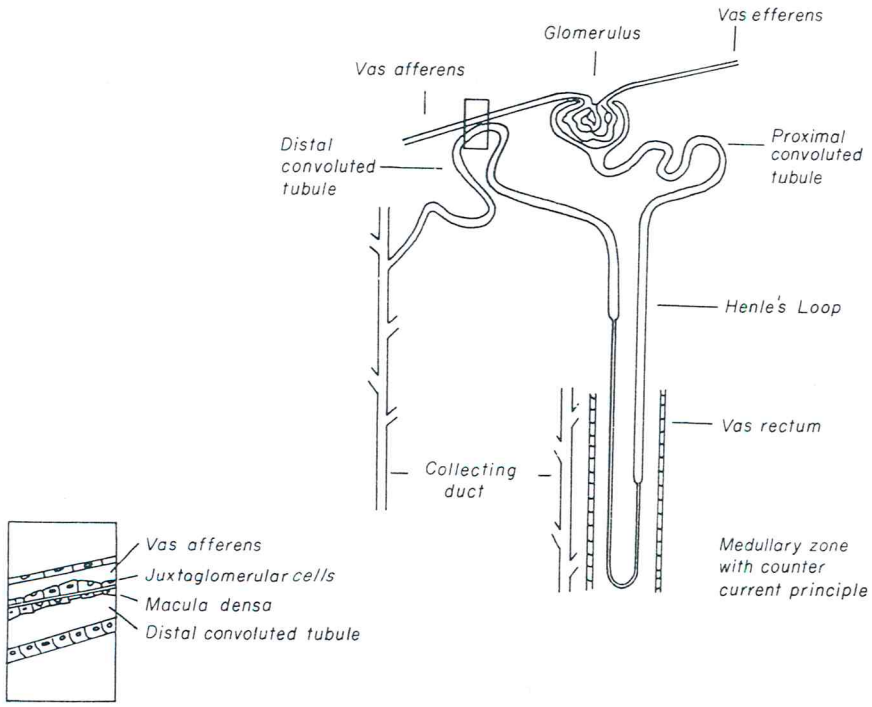


Fig. 32. Schematic representation of a nephron with the various tubular segments, the medullary zone and the juxtaglomerular cells.

blood pressure has been restored. In order to prevent the development of a "shock" kidney at the earliest possible time with developing shock, a forced diuresis with osmotic diuretics (mannitol) is advisable, thereby lowering the Na concentration at the macula densa.

Superimposed upon the localized vasoconstrictor mechanism is a second property of angiotensin, namely, liberation of aldosterone from the zona glomerulosa of the renal cortex.

Collecting Tubules

In the presence of antidiuretic hormone (vasopressin) a considerable concentration of the urine occurs on its passage through the collecting tubules owing to passive water absorption into the hypertonic interstitial space. This process also occurs with urine coming from the short loops of Henle. In the absence of vasopressin the epithelium of the collecting tubules is impermeable to water.

Reabsorption of Bicarbonate; Secretion of Hydrogen Ions. Bicarbonate ions, which are present in the glomerular filtrate and as such are difficult to reabsorb, do not normally appear in urine. There are two reasons for this

1. The following reaction occurs in the tubular cell:

$$CO_2 + H_2O \leftrightharpoons H_2CO_3 \leftrightharpoons H^+ + HCO_3^-.$$

This process is catalyzed by the enzyme carbonic anhydrase.

2. The hydrogen ions formed in the cell are exchanged for sodium ions that are present in the tubular lumen. The H_2CO_3 which then forms in the lumen decomposes into CO_2 and H_2O. Carbon dioxide diffuses easily and is picked up by the tubular cells (Fig. 33).

Potassium Excretion. The potassium in the ultrafiltrate is presumably reabsorbed completely in the proximal tubule, while the potassium that appears in

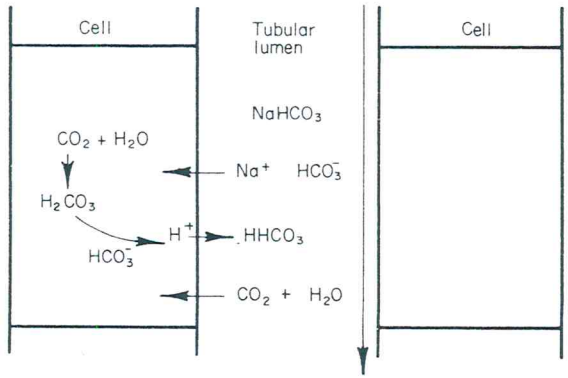


Fig. 33. Schematic representation of the absorption of bicarbonate ions and the excretion of protons.

the urine originates from an exchange with sodium in the distal tubule. Hydrogen and potassium ions compete with each other in this exchange with sodium ions. This results in the following consequences—(1) Increased potassium intake leads to an alkaline urine, as a result of the suppressed secretion of hydrogen ions; (2) if fewer hydrogen ions are available (e.g., under the influence of carbonic anhydrase inhibitors, see below), the excretion of potassium increases; and (3) if there is no sodium in the distal tubule available for ion exchange, potassium excretion is correspondingly diminished. An increased sodium supply to the distal tubule can lead to an enhanced secretion of potassium.

Excretion of Ammonia. Ammonia is released presumably by diffusion from the epithelium of the collecting tubules into the lumen, resulting in the presence of ammonium ions in the urine. With an acidic urine the excretion of ammonium ions is elevated while it is diminished in alkaline urine.

Methods for Testing Diuretics

Diuretics are usually tested in unanesthetized dogs which have been loaded with water or sodium chloride solutions. Water-deprived rats are also frequently used. In order to investigate the mechanism of action more closely, the following parameters are determined in dogs—glomerular filtration rate as measured by inulin clearance and renal plasma flow estimated by means of *p*-aminohippuric acid clearance. In this way it can be established whether and to what extent a drug influences the formation of urine, e.g., how much of the originally filtered sodium appears in the urine. Isolation of tubules after collagenase digestion of connective tissue, puncture and perfusion of single tubular segments, and catheterization of collecting tubules together with the stop-flow technique, can give further information concerning the functions of individual kidney segments and the influence of pharmacological agents. In the investigation of the reabsorption of sodium and water in the distal tubule, the toad's bladder, the epithelium of which corresponds developmentally with the tubular epithelium, has proved to be a suitable model organ. For example aldosterone and vasopressin affect both tissues in an analogous manner.

Diuretics

The term diuretic was initially applied to drugs that caused an increased excretion of urine. However, clinical use of these agents—for instance, in the treatment of edema—has shown it is not the excretion of water alone but the excretion of sodium that is the therapeutically decisive measure. It is more accurate to apply the term diuretics to compounds that increase the excretion of sodium by a direct action on the kidney. Thus, they are also called natriuretics or saluretics. As a result of the decrease in the sodium and corresponding anion concentrations in the extracellular space, there is mobilization and excretion of water and edema disappears. However, in edema-free individuals, the extracellular space can also be diminished. Forced diuresis is not without hazard because in elderly patients a fall

in blood pressure, hypovolemia, and hemoconcentration can result in thromboembolitic episodes.

The following discussion includes a number of diuretics that have been replaced over the years by more effective and less toxic agents. They are mentioned here because of interesting mechanisms of action which have pharmacological and physiological significance, and because under certain specific conditions they can still be utilized as therapeutic agents. The benzothiadiazine derivatives and newly developed compounds are in the forefront of compounds used as diuretics because of their potent diuretic effect and favorable therapeutic index.

Osmotic Diuretics

Just as large amounts of glucose in the urine result in the excretion of considerable amounts of water in a decompensated diabetic, the administration of intravenous doses of mannitol, a hexavalent alcohol, elicits increased production of urine. In contrast to glucose, mannitol is not reabsorbed and appears in the voided urine with a corresponding quantity of water. Such osmotic diuretics have only a slight saluretic effect. However, mannitol is extraordinarily valuable in preventing the development of renal failure in shock (cf. p. 96). An important indication for the administration of hypertonic mannitol or sorbitol (20% solutions) is acute cerebral or pulmonary edema which must be quickly mobilized and excreted by the kidney. In addition, the renal excretion of toxic materials can be accelerated considerably. This effect can be used in barbiturate or salicylate poisoning. In order to initiate and maintain a strong osmotic diuresis, 0.5–2 liters of 10% mannitol are infused in a 6-hr period. This treatment is contraindicated in cases where anuria or severe cardiac decompensation are present. Another hexavalent alcohol, sorbitol, can be used in an analogous way. Earlier, urea was utilized as an osmotic diuretic in daily doses of 30–60 gm orally. This treatment is obsolete.

Purines

Theophylline, caffeine, and theobromine have a weak diuretic effect. This effect is usually not the result of an increase in the glomerular filtration rate which can be detected, but rather of decreased tubular reabsorption. This, in turn, can be related to the higher blood circulation in the renal medulla which leads to increased washout of the interstitial space. In this way the countercurrent system becomes less effective, and the urine contains more water and sodium. Theophylline is more potent than caffeine or theobromine. The action is uncertain and often is diminished upon repetitive administration so that successful osmotic therapy cannot be undertaken with these purines.

Mercurial Diuretics

In earlier times attempts were made to utilize the diuretic effect of mercurous chloride (Hg_2Cl_2). Its action is uncertain and its therapeutic index is very small. Only the introduction of organic compounds containing covalent mercury which do not produce mercury ions in aqueous solution led to active diuretic compounds. They are now obsolete.

Carbonic Anhydrase Inhibitors

In the discussion on the formation of urine it was mentioned that sodium bicarbonate disappears from the tubular lumen due to the action of the enzyme carbonic anhydrase. A large number of sulfonamides are capable of inhibiting carbonic anhydrase, e.g., acetazolamide. The results of this inhibition are those that should be expected theoretically—(1) Fewer hydrogen ions are available for exchange; (2) the exchange of sodium for hydrogen ion is diminished; (3) more sodium, potassium, and bicarbonate ions, and water appear in the urine; (4) the excretion of ammonium ions is impaired; (5) the loss of base produces metabolic acidosis; and (6) this acidosis prevents the further action of the carbonic anhydrase inhibitor, limiting the diuretic effect to about 6–12 hr.

Absorption; Excretion. While the urine becomes alkaline immediately after intravenous injection of acetazolamide, following oral administration the effect begins after about 30 min, reaching a maximum at approximately 2 hr. The compound is excreted in the unchanged form by tubular secretion, up to 80% in 8–12 hr and completely within 24 hr.

Therapeutic Use. Since the introduction of benzothiadiazine derivatives, carbonic anhydrase inhibitors of the acetazolamide type have only limited application. Their natruretic activity is relatively weak and decreases progressively with daily use. They are no longer used to mobilize cardiac edema, but are still useful in short-term supportive therapy of acute glaucoma. This effect is based on diminution of the secretion of aqueous humor. Whether the antiepileptic effect is due to general acidosis (which also has a beneficial effect) or whether there is a specific effect from inhibition of carbonic anhydrase in the brain is not known. Daily oral doses of acetazolamide are between 250 mg and 1 gm. In epilepsy these doses are given once daily; in glaucoma, 250 mg are given every 4 hr.

Side Effects. Since with the exception of glaucoma and epilepsy prolonged therapy with these drugs is no longer usual, only a few side effects are cited here: drowsiness, paresthesia and other neurological conditions, and the alteration of electrolyte metabolism resulting from the drugs' primary effects.

Benzothiadiazine Derivatives

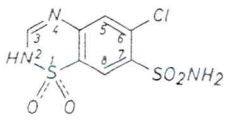
This group of compounds is the result of a further development of compounds related to carbonic anhydrase inhibitors, such as acetazolamide. The SO_2NH_2 group on the ring has been retained and, consequently a certain degree of carbonic anhydrase inhibition remains. However, for the additional new and essential activity, the presence of a chlorine atom (or CF_3 group) in close proximity on the ring is required. The following alterations of the chlorothiazide molecule measurably increase the pharmacological effect: (1) introduction of two hydrogen atoms at the 3,4 double bond (hydrochlorothiazide); (2) exchange of the chlorine in position 6 for a CF_3 group; and (3) substitution of the hydrogen in position 3 by various organic groups.

Mechanism of Action. The most important effect of the benzothiadiazines is the inhibition of the absorption of sodium and chloride, primarily in the distal tubule. This action is similar to that of the mercurial diuretics. Nevertheless, the mechanism of action must be different since it is possible to increase the maximal effect of one diuretic by administration of a second from the other chemical group. The diuretic action of the benzothiadiazine derivatives is not abolished by dimercaprol, while that of the mercurial diuretics is. Neither is the effect of benzothiadiazines affected by metabolic acidosis (as acetazolamide) or alkalosis (as the mercurial diuretics). Only after high doses of benzothiadiazines does one observe additionally an inhibition of carbonic anhydrase that results in an alkaline urine with excretion of bicarbonate. The resulting limited secretion of hydrogen ions and diminished ammonium ion excretion must be localized in the distal portions of the nephron. The excretion of potassium is increased not only with these high doses but also with the lower doses since more sodium is available for exchange in the distal tubule.

The antihypertensive effect of these compounds is ascribed primarily to the increased excretion of sodium; the effect is comparable to that of a salt-free diet. The decrease in the extracellular space is transient and it returns to the predrug level despite continued antihypertensive activity. A certain lowering of vascular tone by these drugs is probable; a direct-acting vasodilator drug has already been prepared from this chemical group. However, it was not useful in therapy since it produced simultaneous sodium retention.

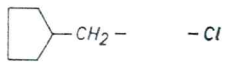
Absorption; Distribution. Chlorothiazide is absorbed from the intestine to the extent of only 10–20% in humans (100% in the dog). This is one reason for its weaker activity when compared to all other chlorothiazide derivatives, which are absorbed from the intestine quickly and completely. In addition, the distribution between the extra- and intracellular spaces is different, being strongly dependent on lipid solubility. It appears that the newer derivatives, being more lipid-soluble and entering the kidney cells more readily, are much more potent than chlorothiazide for this reason also. All these compounds are excreted in the proximal tubule by active secretion.

Therapeutic Use. These derivatives have replaced the mercurial diuretics for mobilizing cardiac edema because of their minimal side effects and the possibility of administering them orally. Some forms of edema found with nephrotic syndrome may also be influenced. They are less suitable for removal of fluid in cases of hepatic cirrhosis, because the potassium loss may lead to hepatic coma. The qualitative effect of all compounds in this group is identical. Since the therapeutic index is also similar, there is no advantage in prescribing agents that have the highest activity per milligram. These compounds (see p. 102 for structures) depending on the seriousness of the disease, are useful alone or in combination with other antihypertensive agents for the treatment of hypertension. In nephrogenic diabetes insipidus they can considerably diminish thirst and the quantity of urine (cf. Antidiuretics, p. 105).



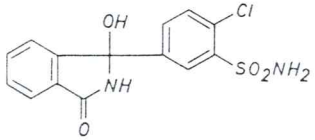
Chlorothiazide
6-Chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
(average dose, 250-500 mg 2 times daily)

Trichlormethiazide
3-dichloromethyl-3,4-dihydro-6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide
(average dose, 2-8 mg/day)

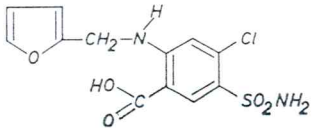


Cyclopenthiazide
3-cyclopentylmethyl-6-chloro-7-sulfamoyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide
(average dose, 0.5-1 mg/day)

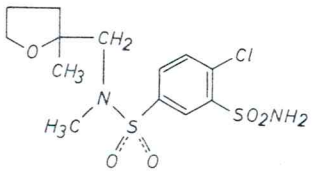
Benzothiadiazine analogs



Chlorthalidone
2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide
(average dose, 100-300 mg/day)



Furosemide
4-chloro-N-furfuryl-5-sulfamoyl-anthranilic acid
(average dose, 40-80 mg/day)



Mefruside
4-chloro-N¹-methyl-N¹-(tetrahydro-2-methyl-furfur-2yl)-m-benzenedisulfonamide
(average dose, 25-75 mg/day)

Side Effects. Stomach disorders, vomiting, and diarrhea occur occasionally. If edema mobilization occurs too intensively and too rapidly, the resulting hemoconcentration can produce a deterioration of the cardiovascular status (danger of thrombosis). The most important and sometimes dangerous side effect is hypokalemia, which is caused entirely by the loss of potassium through the kidney. Overdoses of digitalis or adrenal cortical hormones can aggravate the consequences of this effect. Oral administration of the potassium salts of organic acids—or in the case of hypochloremia, of potassium chloride—prevents this danger (cf. p. 106).

Retention of uric acid occurs which is relatively unimportant and is reversible after discontinuation of the drug. This effect is due to decreased tubular secretion. Only with a disposition to gout is an attack likely to be elicited. The glucose tolerance is also lowered, which may result in prediabetic and diabetic conditions becoming worse. This effect is also reversible. The diabetogenic activity may possibly be lessened by administration of potassium. In a few cases hyponatremia and hypomagnesemia should be taken into account. Serious toxicity such as purpura, agranulocytosis, and hyperparathyroidism is extremely rare.

Analogs of Benzothiadiazine

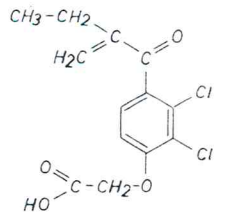
Chlorthalidone, mefruside, and quinethazone (6-sulfamyl-7-chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxochinazoline) contain the same active groups as chlorothiazide and consequently have qualitatively similar effects. Chlorthalidone is absorbed slowly from the intestine, which explains why a single dose can produce an effect of 2 days' duration. The danger of cumulative effects exists with daily doses.

Furosemide inhibits sodium reabsorption primarily in more distal sections; probably the ascending limb of Henle's loop. A maximal chlorothiazide diuresis can be further increased by administration of furosemide. This observation points toward different sites of action for the two diuretics. The onset of the effect of furosemide is rapid after oral doses and only transient. The explanation for the insufficient effect of furosemide in the therapy of hypertension may be that the dosing intervals are too prolonged. In contrast to other saluretics, furosemide increases renal blood flow. The intravenous injection of furosemide and the consequent hemoconcentration can mobilize edema fluid of various origins including cerebral and pulmonary edema. The applications to therapy and side effects of chlorthalidone, quinethazone, and mefruside are the same as those of the benzothiadiazine derivatives. If these agents fail, furosemide may still be effective. Potassium excretion is also increased after furosemide.

Diuretics of Different Chemical Structure

Ethacrynic acid increases the excretion of sodium, chloride, potassium, and water just as do the benzothiadiazine derivatives. It differs in the details of its pharmacological mechanism of action from other saluretics and is effective in cases of refractoriness to benzothiadiazines. The drug acts at the proximal and the distal tubule, as well as at the ascending limb of Henle's loop. It reacts with sulfhydryl group-containing proteins in a manner similar to that of the mercurial diuretics. The tubular, Na/K activated ATPase is inhibited. Under the influence of ethacrynic acid kidney function is changed in such a manner that the urinary osmotic concentration approaches that of the blood, independent of the momentary water–electrolyte balance of the patient—(1) In thirst or during a period of dehydration the reabsorption of free water is inhibited. Because of the effect on Henle's loop, the hyperosmolarity of the medulla is diminished. Therefore the osmotic concentration in the urine does not exceed the isotonic value. (2) In conditions of water diuresis the osmolarity is raised because of the blockade of sodium

reabsorption that usually occurs, so that the free-water clearance in the distal tubule is greatly reduced.



Ethacrynic acid
[2,3-Dichloro-4-(2-methylenebutyryl)-phenoxy]acetic acid
(average dose, 50–150 mg/day)

After oral administration, diuresis commences in about 30 min, attaining a maximum after 2 hr, and lasting about 6–8 hr. Chloride is excreted somewhat more than sodium. Because of the elevated excretion of hydrogen ions, there is a tendency toward metabolic hypochloremic alkalosis. Potassium excretion is increased as it is after the other diuretic agents.

The indications for administration correspond to those for the other saluretics. Because of the rapid and powerful diuretic effect, ethacrynic acid given intravenously is effective, like furosemide, in cases of pulmonary and cerebral edema. Anuria, alkalosis, and cor pulmonale are contraindications. Side effects are essentially the same as for other saluretics. Occasionally the blood level of urea and uric acid increases, and gastrointestinal disorders, as well as hyperglycemia occur.

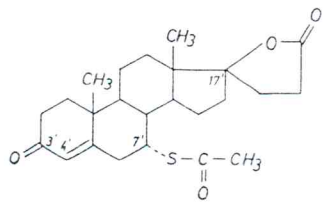
Triamterene (2,4,7-triamino-6-phenylpteridine) increases the excretion of sodium, chloride, and water, while the excretion of potassium is usually diminished. This effect is probably caused by an inhibition of the sodium-potassium exchange in the distal tubule. The use of triamterene is limited because of the pronounced side effects; namely, vomiting, diarrhea, and a general feeling of weakness.

Aldosterone Antagonists

During treatment with very large doses of progesterone a natruresis was occasionally observed despite the presence of sufficient aldosterone. The suggestion that a competitive antagonism was involved could be confirmed by the finding that an even better antagonism to aldosterone could be obtained with other steroids. The compound with the highest activity is spironolactone.

Spironolactone inhibits the effect of aldosterone and also that of deoxycorticosterone on the distal tubule, such that the excretion of sodium and chloride ions is promoted. As a result of the diminished cation exchange in the distal portion of the nephron, the excretion of potassium, hydrogen, and ammonium ions is decreased. No other hormonal effect could be established after administration of spironolactone, except for a few cases of gynecomastia. However in women suffering from kidney diseases amenorrhoea was observed.

Spironolactone is indicated in hepatic cirrhosis with ascites and in some cases of cardiac edema. A combination with other diuretics is frequently useful. In such a case the natruretic effects of benzothiadiazines and spironolactone are additive while the effects on potassium excretion cancel each other. In nephrotic syndrome,



Spironolactone
17-Hydroxy-7-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone, 7-acetate

glucocorticoid therapy can be supported by spironolactone, or if it is inefficacious it can be supplanted by spironolactone.

Spironolactone is given in daily doses of 0.02–0.4 gm, distributed over the day. Since the effect begins only after 2 or 3 days, decision must be reserved until the fifth day as to whether the dose must be lowered or whether other diuretics must be given in combination as the result of insufficient therapeutic effect.

SIDE EFFECTS. Spironolactone is nontoxic apart from the effects connected with its pharmacological usefulness. Hyperkalemia may occur in renal insufficiency while in serious liver disease, particularly if spironolactone is given in combination with other diuretics, hyponatremia can result. Hepatic coma has been improved by spironolactone in some cases. But in some patients coma was precipitated by the drug. Transient, reversible exanthema may occur occasionally.

CONTRAINDICATIONS. Treatment with spironolactone is dangerous in renal insufficiency because of the expected hyperkalemia. Electrolyte balance should be monitored in liver diseases, since stupor and comalike conditions may occur after therapy with spironolactone.

Antidiuretic Agents

Vasopressin

Vasopressin, an octapeptide from the posterior lobe of the pituitary gland, has an important action on the kidney in addition to its direct contracting effect on smooth muscle (cf. p. 45). The antidiuretic and myotropic effects can be dissociated better in synthetic vasopressin analogs than is the case for the natural vasopressin. A water diuresis in humans and in experimental animals, induced by a water load, is interrupted by parenteral administration of vasopressin. If the drug is given early enough, the diuresis is prevented entirely. At the same time the excretion of sodium and chloride is increased. Water diuresis then sets in after a time interval dependent on the dose of vasopressin given initially. The compound increases the cellular permeability for water in the distal convoluted tubule and particularly the collecting tubule. This causes a movement of water from the lumen of the distal tubule into the interstitial space as a result of the sharp gradient in osmotic pressure (for details, see formation of urine, p. 97). Vasopressin activates a renal adenyl cyclase and consequently the formation of 3′,5′-AMP. The increase in water permeability in isolated collecting tubules of warm-blooded animals produced by vasopressin is imitated by this nucleotide. It is also

possible that vascular constriction in the medulla plays some part in the antidiuretic action, since this might lead to a diminished "washout" of the interstitial space that would be equivalent to an improved effectiveness of the countercurrent system. When liquids are withheld (thirst) vasopressin does not inhibit water excretion, but promotes sodium excretion. An antagonism to aldosterone may perhaps be involved in this effect.

The most important indication for vasopressin is diabetes insipidus. Highly purified preparations may be replaced by less expensive total extracts since the contaminating oxytocin does not interfere. In some cases injections may be avoided if a purified preparation is taken as a snuff several times daily. Vasopressin tannate in oil is very useful since it has a delayed absorption time and need be given intramuscularly only once every 2–5 days at a dose of 5 IU.

Vasopressin can be utilized for diagnostic purposes; the ability of the kidney to concentrate urine is tested after an intramuscular dose of 5–10 IU. The effect of such a dose corresponds to approximately 18 hr of thirst.

Saluretics of various types diminish thirst and the amount of urine excreted in diabetes insipidus. Dose levels of hydrochlorothiazide initially of 100 mg, later 25 mg, daily by mouth are effective. The effect cannot be explained solely by the lowered sodium level in the blood since phenylbutazone in daily oral doses of 0.4 gm augments the effect despite increased sodium retention. Some oral antidiabetic agents act in a similar manner.

Electrolytes

The pharmacological importance of some electrolytes, such as potassium, calcium, and magnesium, is discussed in the following section. Other ions, such as sodium or chloride, are not included since they are contained in rather high concentrations in body fluids and can hardly be spoken of or used as pharmacological agents.

Potassium

HYPERKALEMIA. The plasma potassium level is barely increased after oral administration of potassium salts in spite of efficient absorption as the result of quick distribution into tissues and rapid renal excretion. On the other hand, with hemolysis, pronounced tissue destruction, or after parenteral administration of potassium salts, and also after oral doses during renal insufficiency, alarming symptoms of hyperkalemia can occur: myasthenia, finally paresthesia, respiratory depression, but mainly alterations of cardiac function such as bradycardia, disturbances in conduction, and weakening of the contractions. These symptoms are similar to those resulting from vagal stimulation or acetylcholine; however, they are not abolished by atropine. On the other hand, it is possible to abolish the symptoms of potassium poisoning by the administration of calcium, since within a certain range, the ratio of potassium to calcium rather than the absolute serum concentration of potassium maintains balanced cardiac function. In addition,

the increase in glycogen synthesis induced by infusing glucose and insulin, can be accompanied by an increase in the intracellular storage of potassium. Calcium-loaded ion exchangers are capable of exchanging calcium for potassium in the gastrointestinal tract. Elevated blood levels of potassium fall following oral administration of these synthetic resins.

The consequences of hyperkalemia are easily seen on an electrocardiogram (Fig. 34). An elevation of the T-wave appears initially at a serum concentration of 7 mEq potassium/liter; over 8 mEq/liter there is depression of the ST segment accompanied by a normal or slightly shortened or prolonged QT interval. Higher concentrations can elicit heart block, cessation of the heartbeat, or ventricular fibrillation.

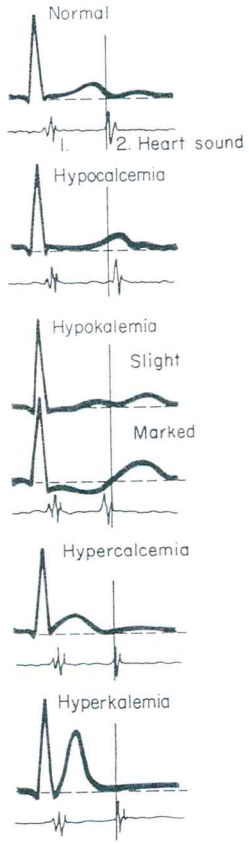


Fig. 34. Schematic representation of typical EKG findings with changes in the blood calcium and potassium levels. The position of the first and second heart tones is also designated.

Hypokalemia. Hypokalemia can be caused by pharmacological agents such as saluretics, glucocorticoids, high doses of digitalis, insulin and glucose in the treatment of diabetic coma, and by chronic use of laxatives. The manifestations of hypokalemia are evident in the same organs as those affected by hyperkalemia. Myasthenia with respiratory depression and finally paralysis, relaxation of smooth muscle as well as decreased heart work and typical electrocardiogram changes are observed (Fig. 34). Hypokalemia can be prevented or abolished by oral administration of potassium salts (corresponding to 4–8 gm of potassium daily). Potassium salts in capsules designed to dissolve in the intestine can lead to severe damage (ulceration and later stenosis) to the intestinal mucosa at the site at which the capsule dissolves. It is therefore recommended that potassium salts be diluted in large volumes for administration. In acute conditions a potassium salt must be given intravenously in doses of not more than 1 gm of potassium per hour.

Calcium

There is an important difference between the behavior of alkali metal ions and those of calcium in the organism. Potassium and sodium ions are always nearly completely in free solution (whether intracellular or extracellular), while only part of the calcium is ionized, the remainder being bound to complexing agents (e.g., organic acids) or to protein. The ionized portion in the serum is about 40% of the total; that in the intracellular space appears to be significantly less. There exists an equilibrium between the two calcium fractions. Some calcium is relatively firmly bound, and it can be accumulated by some structures (along with bone, for example, by erythrocyte membranes). Calcium metabolism is regulated in a very complex manner. It is under endocrine control (cf. parathyroids, p. 219) and dependent on vitamin supply (vitamin D, cf. p. 249).

Pharmacologically, calcium is interesting for several reasons—(1) substitution therapy with calcium, (2) specific pharmacological actions of calcium, (3) the

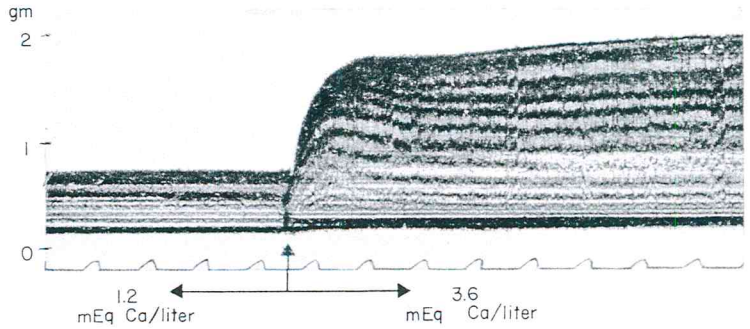


Fig. 35. The dependence of the contractile amplitude on the extracellular calcium concentration. Experiment on the isolated guinea pig atrium; recorded by means of a strain gauge. The atrium is stimulated with a frequency of 2.5 Hz. Time in minutes. At the arrow the calcium ion concentration was raised from 1.2 to 3.6 meq per liter of Tyrode solution; the contractile strength increases markedly.

possibility of relating the actions of other pharmacological agents to changes in the cellular distribution of calcium and (4) therapy of hypercalcemia of varying origin with the sodium salt of ethylenediaminetetraacetic acid. Substitution therapy is always indicated when there exists an acute or chronic lack of calcium. An acute calcium deficit causes tetany, which can be immediately relieved by the intravenous administration of calcium regardless of the etiology. This prompt response does not eliminate the necessity of establishing the cause of the calcium imbalance in order to be able to relate further treatment to it. A chronic deficit results from dietary causes or through an increased requirement (rapid juvenile growth, pregnancy, or lactation). Therapeutically or prophylactically, the required amounts of a calcium salt are taken by mouth (about 5 gm daily for an adult). An intravenous injection, if it is ever necessary, should be carried out extremely slowly since otherwise the concentration that reaches the heart is so high that toxic symptoms develop. Instead of calcium chloride, a local irritant, organic calcium salts such as the gluconate are more suitably used. They can be given intramuscularly.

The specific pharmacological effects of calcium can be best comprehended as representing increases in its physiological function. While calcium deficiency produces an instability of the cell membrane (e.g., spontaneous activity of the motor end plate as in tetany), administered calcium increases membrane stability. This explains the antagonistic effect of calcium in hyperkalemia (increased potassium results in a decreased membrane potential and, thus, in diminished stability). This is especially important to the heart. This membrane-stabilizing effect is further

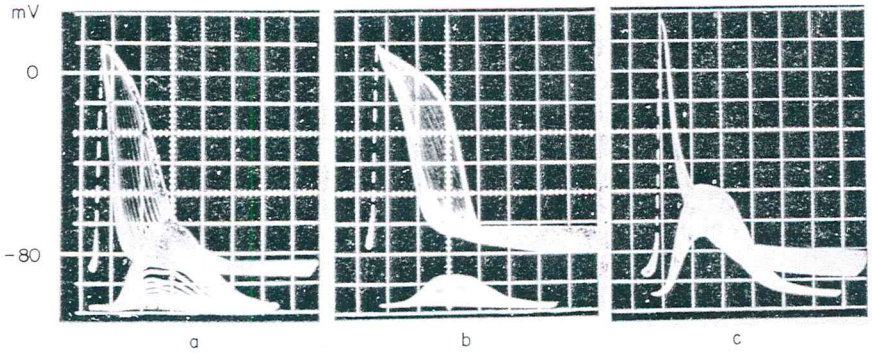


Fig. 36. Changes in the duration of the action potential and the contractile amplitude of an isolated guinea pig atrium induced by ACh (10^{-7} gm/ml) at various extracellular calcium concentrations. The methodology and the manner in which the data are presented are described in Fig. 8. (a) Normal calcium content in the Tyrode solution (1.8 mmoles per liter); acetylcholine shortens the duration of the action potential and reduces the contractile amplitude (experiment identical with that of Fig. 8). (b) Decreased calcium in the solution (0.6 mmoles/liter) the action potential is widened, the contractile amplitude is reduced; the effect of acetylcholine is similar to that found under normal conditions. (c) Increased calcium content in the solution (9.0 mmoles/liter) shortens the duration of the action potential; despite this effect, the muscle contracts more vigorously than under normal conditions. Since acetylcholine can no longer markedly shorten the action potential, the negative inotropic effect is only weakly expressed. Further explanation in the text.

seen with regard to capillary permeability. Calcium decreases capillary permeability, an effect that has found therapeutic application in conditions of increased vascular permeability (e.g., if histamine is liberated during allergic reactions).

Modern concepts concerning the coupling between membrane excitation and the function of intracellular structures (e.g., contractile proteins and storage granules) assign a decisive role to calcium ions. They may be regarded as intracellular transmitter substances that flow into the cell, or are liberated inside the cell, as the result of membrane excitation, and then precipitate the actual cellular activity. For example, this would mean that the stimulation of epinephrine release from the adrenal medulla by acetylcholine requires an intermediate step involving calcium ions. In such a scheme acetylcholine only increases the cellular calcium permeability; calcium passes into the cell and releases epinephrine. A further example: the intracellular concentration of readily available calcium is increased by the administration of cardiac glycosides. The same effect can be obtained by an increase in the extracellular calcium concentration; both result in an increased force of contraction (Figs. 35 and 36). Also in this case the effect of a pharmacological agent is mediated by cellular calcium. Even when the duration of the action potential has been markedly shortened, as in the experimental example by acetylcholine (Fig. 36), resulting in a very short time interval for calcium to enter the cell, an increase in the calcium gradient allows for sufficient activation of the contractile system. Thus the shortening of the process of excitation can be compensated for by the high extracellular calcium concentration.

Magnesium

Although magnesium is an element essential for life, magnesium deficiency is very rare. At present only two syndromes are known in which a magnesium deficiency has been established. One is normocalcemic tetany in which the serum level of magnesium ions has dropped below 0.4 mEq/liter. Since this originates in diminished intestinal absorption of magnesium, only parenteral administration of magnesium results in immediate improvement. Second, low blood levels of magnesium are frequently seen in alcoholics. In delirium tremens erythrocyte and plasma magnesium content are also reduced. Parenteral administration of magnesium salts leads to improvement. Magnesium chloride or magnesium ascorbate in 5–10% solution is suitable for intramuscular or intravenous administration. The central nervous system and the motor end plate are inhibited by administration of large doses of magnesium. A condition similar to that of anesthesia with neuromuscular paralysis occurs. Both functions are normalized immediately by the intravenous administration of calcium, which indicates that the magnesium effect may be due to displacement of calcium from sites necessary for its function. "Magnesium anesthesia" has no practical application, since autonomic centers and respiratory muscles are paralyzed.

Solutions for Infusions

A careful observation of electrolyte balance in many diseases and surgical operations has confirmed that the chances of improvement are considerably better if

abnormalities in the composition of body fluids can be abolished by the administration of suitable electrolytes. Depending on the individual case, isotonic salt solutions with varying ratios between sodium, potassium, and calcium ions, or isotonic sugar solutions (glucose, fructose) or mixtures of these solutions must be used. A large number of solutions for infusion is available commercially. They are generally given intravenously. If this is not possible, subcutaneous administration can be accelerated by the addition of hyaluronidase. This enzyme splits hyaluronic acid, a mucopolysaccharide acid which is an important component of the cementing substance in connective tissue. The activity of the hyaluronidase results in a loosening of the tissue and provides more free space for the distribution and absorption of infused solutions. Every case of infusion therapy requires an individual and constant control of electrolyte and water balance. Elevation of the osmotic pressure in the extracellular space leads to redistribution of water in this space and accordingly also in the vascular system. Mannitol and sorbitol are best suited for this purpose, and additionally they cause an osmotic diuresis (p. 99). Such osmotherapy is recommended to reduce the pressure of the cerebrospinal fluid in cerebral edema, during operative procedures on the brain, in acute cases of glaucoma, and in pulmonary edema. Up to 500 ml of a 20% solution may be infused. Therapy can eventually be further supported by infusion of hypertonic, salt-free dextran solution. Urea is now obsolete for osmotic therapy.

Gastrointestinal Tract

Stomach and Intestines

Astringents

Astringents are substances that cause precipitation of protein in superficial layers when applied to mucous membranes or wounds, providing a sealing of the surface and resulting in a slight shrinkage of the tissue. Such compounds are indicated for the local treatment of inflamed membranes and wounds; the therapy is nonspecific and cannot replace more specific treatment.

Two groups of astringents are used clinically: (1) preparations containing tannin, such as tannic acid, and a whole series of galenic preparations (e.g., tincture of myrrh) and (2) dilute solutions of metal salts such as silver nitrate, zinc sulfate, bismuth subgallate, and aluminum acetate. The concentration of the metal salt is very important since higher concentrations have a cauterizing effect.

Antiphlogistic Agents Influencing Mucous Membranes

An extract of licorice has been used with doubtful success in the therapy of peptic ulcer. More convincing results were obtained after the isolation of some of the active principles, especially glycyrrhetinic acid. Carbenoxolone, the hemisuccinate of this acid, upon direct contact with the gastric mucosa increases mucus production in the stomach. This effect contributes, in ambulant patients, to an

accelerated healing of peptic ulcers. Successful results in the treatment of duodenal ulcers remain doubtful since it is difficult to apply carbonoxolone at the required site of action even in a preparation soluble in the intestine.

Antacids

Antacids are pharmacological agents capable of neutralizing excess stomach acid. Their use is indicated in hyperacidity and in gastric or duodenal ulcers secondary to hyperacidity.

Aluminum hydroxide gel, $Al(OH)_3$, reacts with hydrochloric acid to form $AlCl_3$; 1 gm of dried gel neutralizes approximately 250 ml of 0.1 *N* HCl. The astringent effect of aluminum chloride and its alkaline reaction products which are formed in the intestine can cause slight constipation. The very large surface area of the aluminum hydroxide gel can bring about the adsorption of enzymes, resulting in a loss of their physiological function. The absorption of phosphates from the intestine is also diminished. The administration of $Al(OH)_3$ for several months can prevent the formation of stones composed of phosphate salts in the renal pelvis.

Diamagnesium trisilicate hydrate, $Mg_2Si_3O_8 \cdot nH_2O$, is an inorganic compound that reacts with hydrochloric acid to form $MgCl_2$ and SiO_2; 1 gm neutralizes up to 150 ml of 0.1 *N* HCl. The onset of action is slower than that of aluminum hydroxide gel.

Sodium bicarbonate, $NaHCO_3$, in contrast to the above compounds which react slowly with hydrochloric acid, reacts rapidly, liberating carbon dioxide. If an excess of sodium bicarbonate is given, the stomach contents become alkaline which in turn stimulates renewed, compensatory acid production. The effect of sodium bicarbonate is correspondingly quite short and in addition provokes unpleasant gas production. Also, sodium ions are absorbed ($NaHCO_3 \rightleftharpoons Na^+ + HCO_3^-$) and shift the acid-base equilibrium to the alkaline side, since the anion is exhaled as carbon dioxide. For these reasons the treatment of hyperacidic conditions with sodium bicarbonate is not recommended.

Acids

A deficiency of hydrochloric acid production in the stomach leads to insufficient predigestion of proteins since pepsin has a pH optimum of about 2.2. Indigestion after protein-rich meals can be the result. There are two alternatives for the treatment of this condition—(1) administration of acids such as hydrochloric acid (25%, diluted 15–40 drops per glass of water) or preferably citric acid (crystalline powder, single dose 0.25–1.0 gm) (2) and administration of proteinases that have a pH optimum in neutral or weakly acidic solution. One can further attempt to stimulate acid production reflexly or by direct action on the mucosal lining of the stomach. This can be achieved through the administration of bitter substrates ("bitters").

It also should be pointed out that histamine and gastrin (a peptide of 17 amino acids which can be extracted from the pancreas and gastric mucosa as well as synthesized chemically) are very strong stimulants of gastric juice production.

Pentagastrin, which contains terminal essential amino acid residues of gastrin, may be used instead of gastrin itself. The importance of these compounds in the diagnosis of pernicious anemia is discussed on page 81. Gastrin and pentagastrin increase the tone in that part of the esophagus adjacent to the cardia, and decrease tone in the region of the ileocecal valve.

Laxatives

Laxatives are pharmacological agents that increase the rate at which the intestinal contents are transported, leading to more rapid defecation. There are basically two indications for the use of laxatives.

1. Treatment in acute cases—This includes the combination of obsolete anthelminitics and laxatives designed to remove the anthelmintic (which is toxic to the patient as well as the parasites) as quickly as possible from the intestine, and the administration of laxatives in cases of poisoning to shorten the time available for absorption of the noxious agent.
2. The treatment of chronic constipation—The use of laxatives for this purpose is very widespread, and the task of the physician more frequently is to stop such "therapy" rather than recommend it. Long-standing use of laxatives can develop intestinal dysfunction ("laxative colon" seen radiographically). Chronic use of doses which elicit diarrhea can lead to intestinal atony and muscle weakness because of the resultant losses of sodium and potassium. Even the plasma protein level can fall as the result of continuous loss of protein. Chronic constipation can have organic origins; however, it is in general a functional disturbance. In the latter case treatment without laxatives should be attempted (change of habits, introduction of a conditioned reflex, etc.). At the same time it must be pointed out to the patient that following withdrawal from a daily dose of laxatives, a compensatory pause in the frequency of defecation must result. The intestine is empty, it takes several days to fill the rectum sufficiently before the defecation reflex again occurs. The modern low-fiber diet is one of the main reasons for so-called chronic constipation. It has its origin only in the disproportion between the patient's expectation and the supply of roughage in the diet. One indication for chronic use of laxatives are anal complaints. In this case it is important that the feces be soft.

Intestinal Irritant Laxatives

Primary Activity on the Small Intestine. Castor oil (oleum ricini) has as one of its main constituents the triglyceride of ricinoleic acid [$CH_3(CH_2)_5$-$CHOHCH_2CH{=}CH(CH_2)_7COOH$; 12-hydroxyoleic acid]. The triglyceride itself is inactive; only after hydrolysis by lipases in the digestive fluids is the active, free acid available. The laxative effect of ricinoleic acid can be counteracted by antihistamines in animal experiments. Therefore, it is supposed that the intestinal stimulation by ricinoleic acid results from the liberation of histamine. Therapeutic doses of castor oil (10–30 ml orally) have no side effects, and the occasional intestinal pain is an expression of the therapeutic effect. Its effect is very certain, and the intestine is cleared within 1–4 hr.

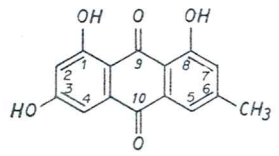
Activity on Large and Small Intestine. This group includes the so-called resinous drugs, which all have a rather drastic cathartic effect. The use of these agents cannot be recommended since irritation of the mucous membrane may progress to enteritis. In pregnant patients an abortion is to be feared. The hydrolysis of these resins liberates hydroxylated fatty acids, which indicates a certain similarity to the effects of castor oil. Their activity is also inhibited by antihistamines. The following natural products may be considered drugs of the resinous group: jalap resin (resina jalapae), podophyllum, and colocynth.

Activity Chiefly on the Large Intestine. A number of drugs contain anthraquinone derivatives possessing a laxative action: senna leaves, rhubarb, cortex frangula bark, cascara sagrada, and aloe. The anthraquinones are bound to sugar molecules as glycosides. The derivative remaining after removal of the sugar is called an emodin. The structures of two emodins are given below as examples.

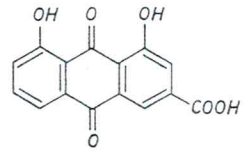
After oral administration, the glycosides are slowly hydrolyzed in the intestinal tract, the derived anthraquinones are reduced to anthrones, which in turn are converted to anthranols, which are the active agents. They are absorbed to a slight extent and excreted in the urine (coloration of alkaline urine) and in milk (laxative effect on the nursing infant). The emodins increase peristalsis exclusively in the large intestine. The effect sets in after about 6–10 hr, since this time is required for passage through and absorption from the small intestine or for excretion into the large intestine. The emodins are recommended for use in all cases where a prompt effect is not required. An exception is aloe, which contains poisons irritating to the intestine and kidney in addition to the glycoside; its use is not recommended.

Apart from the galenic preparations, the pure glycosides from senna leaves are commercially available. The synthetic 1,8-dihydroxyanthraquinone has relatively weak activity.

Phenolphthalein also stimulates mainly the large intestine with rather rare side effects due to hypersensitivity (diarrhea, colic, and occasionally collapse or drug exanthema). The related substance bisacodyl, from which the acetate moieties are removed in the intestine, acts in a manner similar to phenolphthalein. These compounds probably act by preventing water absorption and ion transport in the intestinal wall.



Emodin from the bark of the alder buckthorn
1,3,8-Trihydroxy-6-methylanthraquinone



Rhein from rhubarb
1,8-Dihydroxyanthraquinone-3-carboxylic acid

Sulfur, which is reduced to hydrogen sulfide by intestinal bacteria, also stimulates peristalsis. The quantity of hydrogen sulfide produced is dependent upon the surface area of the sulfur particles. The hydrogen sulfide absorbed may adversely affect the patient; therefore, the use of sulfur is obsolete.

Bulk-Forming Laxatives

The physiological stimulus for peristaltic waves and, thus, for transport of the intestinal content is the intestinal filling pressure. If the internal pressure is elevated, thereby increasing the stretch on the intestinal smooth muscle, increased peristalsis of the musculature occurs. This physiological mechanism is the basis for the activity of pharmacological agents in this group.

Osmotically Active Laxatives. A salt can have laxative action only if at least one of the ions that exists in aqueous solution cannot penetrate the intestinal mucosa and is thus retained in the intestinal lumen for a reasonably long time. If only the anion (such as SO_4^{2-}) is not absorbed, an equivalent amount of cation (e.g., Na^+) must also be retained. Since the body attempts to adjust all body fluids, including the intestinal content, to the osmotic pressure of the blood, an osmotic laxative will lead either to passage of water into the intestine, if the solution was originally hypertonic, or to absorption of water, if a hypotonic solution has been administered. The onset of action after such laxatives depends not only on the quantity of salt given but also on the volume of the ingested liquid. It takes longer to stimulate the stretch reflexes after administration of hypertonic solution than after the intake of the same salt quantity in a larger volume of liquid (approximately isotonic solutions are optimal). Administration of hypertonic solutions can also lead to defecation by means of reflexes. They also result in a loss of body water. Salts that are most suitable are sodium sulfate (Na_2SO_4, 10.0–20.0 gm; isotonic solution, 3.2%) and magnesium sulfate ($MgSO_4$, 10.0–20.0 gm isotonic solution, 4%). These laxatives act promptly and with certainty and are without side effects. Other salts, such as potassium-sodium tartrate or disodium phosphate, are superfluous. Potassium bitartrate may be given to patients who must be maintained on a low salt diet. Citrates are also poorly absorbed. Analogously, the hexavalent alcohols, mannitol and sorbitol, act in basically the same manner in that they are difficultly absorbed. Their use is accompanied by potassium loss. Two hundred grams of mannitol in 1 liter of water given by mouth over a 2 hr period cause a diarrhealike defecation of almost 4 liters. Instead of dialysis this procedure may be followed in emergency cases if diuretics are ineffective, provided that the clinical picture is one of pronounced water retention without too marked an increase in BUN (blood urea nitrogen).

Bulk Furnishers. Compounds that are not absorbed and undergo volume expansion because they take up water also elicit increased peristalsis. Suitable compounds are agar (10.0 gm several times daily) and carboxymethyl cellulose. These swelling agents must be given with large amounts of liquid since otherwise there is the danger of obstruction of the intestinal lumen (danger of ileus). Vegetable diets with an extremely high cellulose content accomplish the same purpose.

Lubricant Laxatives

Liquid petrolatum is a mixture of indigestible aliphatic hydrocarbons. The oily nature of the substance softens the contents of the colon and lubricates it. There are, however, side effects that restrict the use of liquid petrolatum to short periods. Loss of appetite and intestinal disturbances set in. In addition, a large amount of

petrolatum may be absorbed if it is well emulsified, leading to foreign-body reactions in the abdomen. Furthermore, there is a decreased absorption of fat-soluble vitamins. This laxative should definitely be avoided during pregnancy.

Anthelmintics

Anthelmintics are chemotherapeutic agents with a specific effect on parasitic worms. In the temperate zones only worm infestations of the intestine are of practical importance, and the following section only deals with the therapy of infections with such parasites as flatworms (cestodes) and roundworms (nematodes).

Several experimental methods exist for testing the activity of compounds as anthelmintics. Some worms when kept in a suitable medium exhibit mechanical activity *in vitro* which can be recorded. Anthelmintics usually produce initial stimulation followed by paralysis of the worms. Deliberate infection of experimental animals also can be used to provide a means of testing anthelmintic activity.

Drugs Effective against Flatworms

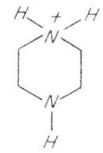
Extract of male fern, or the isolated active agent, filicic acid, which formerly was often used, should no longer be employed because in addition to the local irritation there is a possibility of serious absorptive poisoning (convulsions, motor paralysis, loss of consciousness, and cardiac damage). The simultaneous administration of a laxative with this drug is compulsory. Modern pharmacological agents which are more potent and less toxic have largely replaced this drug. The antimalarial drugs such as quinacrine which were long used in therapy for their anthelmintic activity are also obsolete.

Currently, two very good antitaenial drugs exist, niclosamide *N*-(2′-chloro-4′-nitrophenyl)-5-chlorosalicylamide, and a mixture of tin, its oxide, and its chloride. The only side effects appear to be irritation of the gastric mucosa. Therefore, the tablets should be given after meals. A laxative is not necessary. Niclosamide seems to interfere with the carbohydrate metabolism of the parasite; it promotes glycolysis and blocks the citric acid cycle, resulting in an increase in the lactic acid concentration in the flatworm. Furthermore, the compounds which protect the worm against intestinal proteases are inactivated.

Drugs Effective against Roundworms

Within this group of drugs the use of many earlier agents has become obsolete, including oil of chemopodium, its main active component, ascaridol, and santonin.

The agent that is now most highly recommended for the control of nematode infections is piperazine. According to electrophysiological investigations, it stabilizes the membrane potential of the worm musculature so that an effect develops which is comparable to that of curare. Piperazine is a base, and is used in the form of a salt. Although piperazine is well absorbed from the intestinal tract, the concentration remaining in the intestine after oral administration is also sufficiently high to clear oxyuriasis (pinworm infestations). The dose in adults is 1.0 gm twice daily



Piperazine

for several days (90% cure of ascariasis). In oxyuriasis the same treatment is repeated after 1 week (95% cure). Fasting or the administration of laxatives is not required during a course of treatment. Rarely, piperazine produces some slight side effects such as diarrhea, urticaria, or central nervous system effects (tremor, ataxia, disturbed accommodation); in children with cerebral damage the central side effects are more frequent with even the occurrence of convulsions. Long-lasting damage has not been observed. The intake of alcohol should be avoided during treatment with piperazine.

The cyanin dye pyrvinium pamoate has even better activity than piperazine against pinworms. It blocks enzymes in the oxidative metabolism of the parasites. Side effects such as nausea and vomiting occur very seldom. The feces become red in color. The dose for children and adults is 5 mg/kg once daily by mouth.

Bephenium hydroxynapthoate (*N*-benzyl-*N*,*N*-dimethyl-β-phenoxyethylammonium-3-hydroxy-2-napthoate) is active against hookworms, particularly *Ancylostoma duodenale*. In epidemics of infection with *Ancylostoma duodenale* and *Necator americanus* in the tropics, treatment with carbon tetrachloride or with the less toxic agent, tetrachloroethylene, has been found useful. In some cases of the disease the therapy discussed above is preferable.

Thiabendazole (2-[4′-thiazolyl]-benzimidazole) has a broader spectrum of activity in comparison with the other anthelmintics. Apart from ascaris and pinworm, *Trichuris trichiur* (whipworm) and *Strongyloides stercoralis* are also eliminated. Even in some cases of trichinosis, treatment has proved successful. Gastrointestinal side effects are frequent and disturbances of the central nervous system may also occur. In case of simple worm infections a 1-day treatment with 3.0 gm thiabendazole is sufficient.

The Liver

The therapeutic possibilities with liver parenchymal diseases are rather limited. The administration of large amounts of glucose or fructose (in hepatic coma up to 400 gm/24 hr) is a symptomatic measure. Solutions of 5% are used for intravenous infusions; 8% solutions are given orally. A so-called "protective liver therapy" with choline or methionine is rational only if there is a deficit in one of those compounds due to an insufficiency in the diet. A genuine therapeutic effect beyond the favorable effect of a protein-rich diet as such cannot be demonstrated. The administration of liver extracts and hydrolysates represents placebo therapy. Vitamin preparations are only meaningful in cases of vitamin deficiency. Glucocorticoids have good symptomatic effects in viral hepatitis and some cases of chronic hepatitis.

Hepatic coma can sometimes be managed with large doses of prednisolone. (For the lowering of the blood ammonia content by neomycin, see p. 286; for the role of the liver in the biotransformation of drugs, see p. 324).

The secretion of bile by the liver can be increased by the administration of "choleretics." The most potent "choleretic" agent is dehydrocholic acid, which initiates the secretion of highly dilute bile. Dehydrocholic acid should not be used in parenchymal diseases because the elevated secretory function imposes an additional load upon the liver. The compound is absorbed well by the intestinal mucosa. For this reason it is not useful to administer it orally in obstructive jaundice with the intention of improving the absorption of fats, vitamins, etc. The dehydrocholic acid itself is absorbed and then contributes to a further increase in the content of bile acids in the blood and tissues. A choleretic agent such as dehydrocholic acid appears to be indicated only in cases where "hydrodynamic" considerations make an increased flow of bile in the biliary ducts desirable; for example, in the case of very small gallstones in the bile duct. Egg yolk and saline purgatives effect clearing of the gall bladder by a reflex action originating from the small intestine (cholagogues). Following oral administration, cholestyramine, a nonabsorbable anion-exchange resin, binds bile acids in the gastrointestinal tract, thereby preventing in part their absorption and continued reentry into the enterohepatic cycle. It decreases the elevated levels of bile acids in the blood and thus alleviates some symptoms accompanying icterus, in particular the pruritus. With longer treatment, the danger of interference with fat absorption and its consequences exists.

CHAPTER 2

MOTOR SYSTEM

Motor End Plate

The motor end plate is at the junction between the motor nerve fiber and the skeletal muscle cell. Since the stimulus conducted along the nerve cannot bridge the anatomical discontinuity, a chemical compound mediates this transmission process. The motor end plate is rather small for a contact point between two different tissues, but due to membrane folding, it has a large surface area. The synaptic cleft (about 500 A in width) is bridged by diffusion of acetylcholine (structure on p. 9), which is very rapidly released from storage vesicles at the nerve ending upon arrival of the incoming stimulus.

The ion permeability of the end plate membrane is then altered by acetylcholine. The sodium conductance, especially, increases markedly, which leads to end plate depolarization (see the schematic presentation in Figs. 37, 38), which in turn initiates a propogated excitation of the muscle membrane once a critical threshold has been achieved. The end plate membrane contains structures (receptors) that react with acetylcholine and precipitate alterations in the properties of the membrane discussed above. This property is limited to the end plate. The muscle cell membrane, apart from the end plate, is not depolarized by acetylcholine. This "stability" of the muscle cell membrane is lost upon chronic denervation (beginning about 5 days after the motor nerve has been severed), and the whole surface of the muscle cell then reacts similarly to an end plate (Fig. 39). Chronically denervated skeletal muscle preparations can thus be used as a model for the end plate in pharmacological experiments (Figs. 39, 40). Acetylcholine, which is released by nerve stimulation and also spontaneously in small quantities (miniature end plate potentials), is very rapidly hydrolyzed by "true" acetylcholinesterase, which is con-

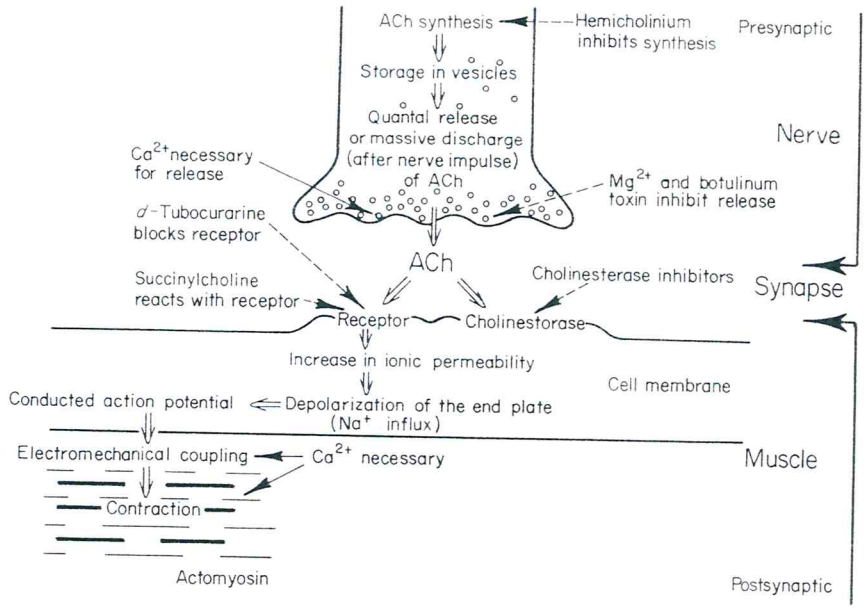


Fig. 37. Schematic representation of events in the region of the neuromuscular synapse. See the text for details.

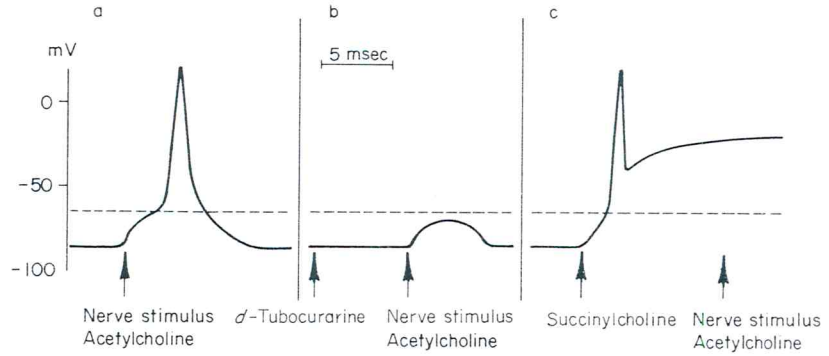


Fig. 38. Schematic representation of the membrane potentials at a motor end plate; the potentials have been monitored with an intracellular microelectrode. (a) Under normal conditions. (b) In the presence of a membrane-stabilizing compound, *d*-tubocurarine, and (c) in the presence of a depolarizing compound, succinylcholine. See the text for details.

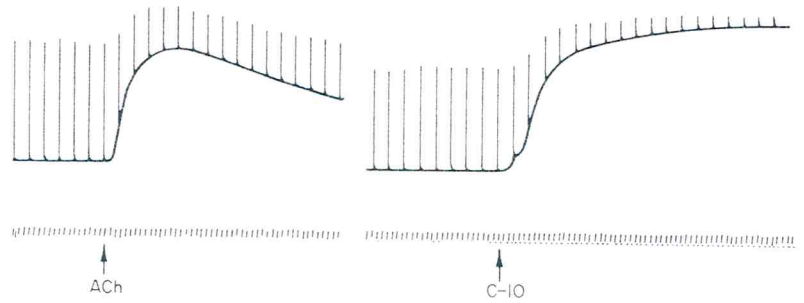


Fig. 39. The effect of depolarizing compounds on a chronically denervated skeletal muscle. The contractions of the isolated hemidiaphragm of the rat were produced by direct stimulation and recorded by means of a strain gauge. The stimulus frequency was 15 per minute; stimulus duration was 15 msec. Time on the lower margin in seconds. The hemidiaphragm was denervated 8 days before the experiment by extirpation of the phrenic nerve. The addition of acetylcholine 10^{-6} gm/ml (ACh) and decamethonium 5×10^{-5} gm/ml (C-10) results in a contracture of the muscle which is an indication of the depolarization of the cell membranes.

tained in large amounts in the end plate (concerning cholinesterase, see p. 11). The neurotransmitter thereby is rendered biologically inactive. This system of transmission of stimuli from nerve to skeletal muscle can be interrupted presynaptically or postsynaptically in various ways. Presynaptically either acetylcholine synthesis can be inhibited by hemicholinium (*p*,*p*'-bis[1-methyl-3-hydroxymorpholinyl-3]diphenylbismethylhydroxide) or the liberation of acetylcholine can be prevented. The latter can be induced by a lack of Ca^{2+} ions, an excess of magnesium ions, potent local anesthetics, or by botulinum toxin (cf. Fig. 37). For practical purposes, two classes of drugs have been found which can be used therapeutically: (1) drugs

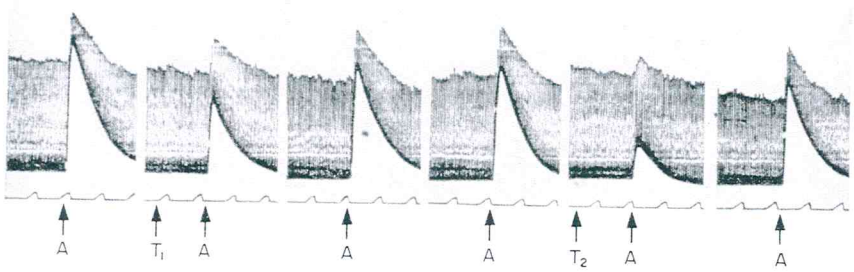


Fig. 40. The effect of *d*-tubocurarine on the response to acetylcholine in chronically denervated skeletal muscle. Methodological details are as in the previous figure. The velocity of the recording is, however, slower, the time marks on the lower margin are in minutes. The drugs were washed out when the recording was interrupted. A, addition of acetylcholine 10^{-6} gm/ml; T_1 and T_2, addition of *d*-tubocurarine, 10^{-7} and 3×10^{-7} gm/ml, respectively. Acetylcholine, because of its depolarizing effects, produces a contracture which can be inhibited by *d*-tubocurarine in a concentration-dependent manner by its membrane-stabilizing effect.

which react with the acetylcholine receptor (neuromuscular blocking agents) and (2) drugs which react with cholinesterase (inhibitors).

Neuromuscular Blocking Agents

Mode of Action

The reaction of drugs with acetylcholine receptors at the end plate membrane may produce two different results: (1) either the drug receptor complex leads to the same result as the acetylcholine-receptor complex—namely, a depolarization (intrinsic activity is present) or (2) the new complex is biologically inactive (without intrinsic activity) and prevents the reaction of the physiological transmitter, acetylcholine, with the receptor (competitive inhibition, prevention of depolarization). If depolarization is prevented, a paralysis of skeletal muscle results because stimulation of the somatic nerve is no longer transmitted to the muscle (see Fig. 38). The other type of response results in depolarization and consequently the muscle fiber goes through a contraction cycle. Further events now depend on the rate at which the agonist disappears from the biophase (the compartment immediately surrounding the receptor). Acetylcholine is split within milliseconds by acetylcholinesterase so that immediate repolarization is possible and the end plate is again ready to be stimulated. If degradation is slower, the end plate membrane is kept in a partially depolarized state such that any acetylcholine released by the next nerve stimulus contacts an already depolarized end plate so that a new action potential

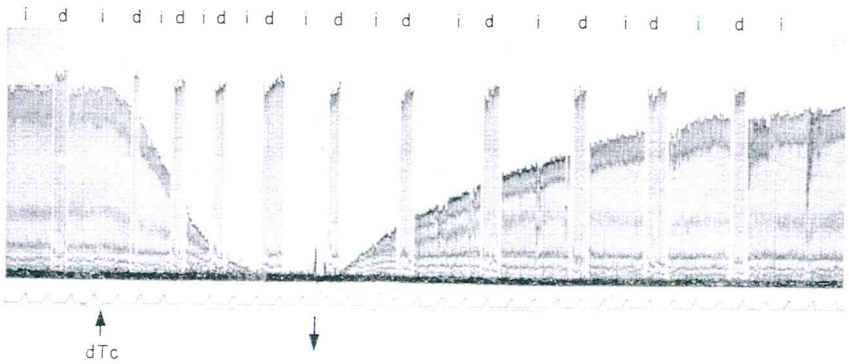


Fig. 41. The effect of *d*-tubocurarine on a nerve muscle preparation. The contractions of a rat hemidiaphragm are recorded by means of a strain gauge. The diaphragm is stimulated either directly (d) or indirectly (i) by means of the phrenic nerve. The stimulation frequency was 15 per minute with a duration of 5 msec for the muscle and 0.2 msec for the nerve. Stimulus strength was always supramaximal. Time on the lower margin in minutes. Neuromuscular transmission was completely blocked in a few minutes following addition of *d*-tubocurarine, 10^{-6} gm/ml (dTc), while the contractions in response to direct stimulation were completely unaffected. Following washout (downward arrow) neuromuscular transmission is completely restored.

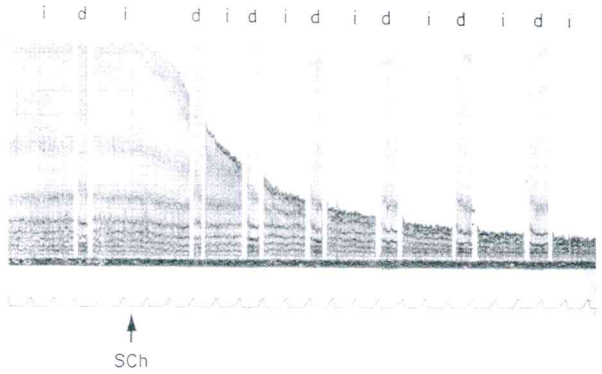


Fig. 42. The effect of succinylcholine on a nerve-muscle preparation. Methodological details are in the previous figure. Neuromuscular transmission is almost completely blocked by the addition of succinylcholine 2×10^{-6} gm/ml (SCh) while contractions in response to direct stimulation remain unaffected.

cannot be elicited (Fig. 38). Neuromuscular blockade with skeletal muscle paralysis is the result.

The one-time stimulation of each muscle fiber on application of a neuromuscular blocker of the depolarizing type does not lead to the development of appreciable tension by the whole muscle because there is a lack of coordination in time in the contractions of the separate fibers. The result is merely transient muscular fasciculations.

The inhibition of neuromuscular transmission by drugs of either the competitive or depolarizing type is very specifically located at the end plate. The muscle itself remains fully functional. Experimentally this can be shown in so-called nerve–muscle preparations, in which one pair of electrodes stimulates the nerve and thereby indirectly the muscle via the end plate mechanism, while a second pair stimulates the muscle directly. Figures 41 and 42 show such experiments with the isolated phrenic nerve-diaphragm preparation of the rat. Additionally, it is possible to distinguish between the two types of inhibition (competitive and depolarizing) in animal studies. As mentioned above, the behavior of chronically denervated skeletal muscle is identical to that of an end plate; any depolarizing substance elicits, *in vitro*, a contracture (cf. Fig. 39) while competitive agents prevent such a contracture; an example of such an experiment is shown in Fig. 40.

Clinical Use

Neuromuscular blockers can always be used if diminished skeletal muscle motor activity is required. The chief application is in the modern practice of anesthesia in which the necessary muscle relaxation is obtained, not by high anesthetic levels, but by the use of a neuromuscular blocker. Such drugs are also of great value

in the treatment of poisonings and diseases connected with increased motor activity (strychnine, tetanus). A further application is in psychiatric electroshock therapy. These drugs prevent possible bone fractures that may otherwise occur as the result of the extreme force developed by the skeletal musculature during a shock-induced convulsion.

In the use of neuromuscular blockers two points should be kept in mind at all times—(1) The skeletal muscle of various body regions is not equally sensitive to these drugs. The respiratory muscles are usually somewhat less sensitive than other skeletal muscles, but in principle the activity of the respiratory muscles can be inhibited in the same way as that of other groups. For this reason, possible paralysis of the respiratory musculature must always be considered when such therapy is employed. The single, rational procedure to counteract this purely peripheral respiratory depression is artificial respiration. Centrally acting analeptics or electric stimulation of the phrenic nerves are useless. (2) Neuromuscular blocking agents have no effect on the central nervous system, and consciousness is fully retained. This means that such drugs are no substitute for anesthesia. One should consider that the patient perceives the oxygen deficiency resulting from inhibition of the respiratory muscles (shortness of breath) but is unable to do anything about it. These very unpleasant subjective feelings owing to the coexistence of full consciousness and inability to initiate any muscle activity have been described by scientists who served as experimental subjects and were fully curarized.

Competitive Inhibitors

Curare is the name for the South American Indian arrow poison. It contains alkaloids from strychnos and chondrodendron species. Of these, *d*-tubocurarine, isolated from tube-curare, has attained particular importance for medical purposes. Apart from the competitive action at the postsynaptic acetylcholine receptor *d*-tubocurarine also affects the presynaptic structure slightly; the amount of acetylcholine liberated per stimulus is reduced. Another alkaloid with neuromuscular activity, toxiferine, isolated from calabash curare, is also prepared by South American Indians. Its allyl derivative (diallyl-bisnortoxiferine) is relatively short acting. *d*-Tubocurarine is not active when administered orally, since its rate of absorption from the intestine is slower than its rate of excretion. Parenteral administration leads to paralysis of skeletal muscles, the most sensitive groups of muscles being those innervated directly by the cranial nerves, especially the external eye muscles. The diaphragm has the highest resistance. The effect of a single dose (5–30 mg intravenously in the adult) which results in complete neuromuscular blockade, disappears after 20–40 min. The rate of elimination is, however, relatively slow, as evidenced by the fact that a second injection of the same dose up to 24 hr after the first has a stronger effect. The largest proportion of the *d*-tubocurarine is metabolized in the body and rendered biologically inactive; about one third is excreted unchanged via the kidney. Since the individual sensitivity to *d*-tubocurarine varies considerably, the dose has to be individually determined. Very rarely *d*-tubocurarine in therapeutic doses results in the release of tissue stores of histamine, which produces dangerous complications. The released histamine can

cause a decrease in blood pressure, increased bronchial secretion, and (most important) a dangerous bronchial spasm. Ganglionic transmission is not influenced by the doses necessary for muscle paralysis.

To counteract an overdose of *d*-tubocurarine, or to shorten its duration of action, cholinesterase inhibitors can be injected as antidotes. Thereby a higher concentration of acetylcholine is attained at all cholinergic synapses, including the motor end plate. This produces a shift in the equilibrium in favor of the agonist. Simultaneously the tonus of the parasympathetic system is augmented. For this purpose neostigimine is particularly suitable.

A synthetic derivative of *d*-tubocurarine is dimethyltubocurarine (produced by methylation of the phenolic OH groups), which has the same effect as the starting material but is twice as potent.

The *d*-tubocurarine molecule has given rise to considerable speculation and experimentation concerning structure–activity relationships. The biologically active groups in this complex molecule are both quaternary nitrogen atoms, linked by molecular bridges of 10 atoms each, and 14 Å distant from each other. The synthesis of compounds with these two structural features has led to new drugs that have a specific affinity for the acetylcholine receptor at the motor end plate.

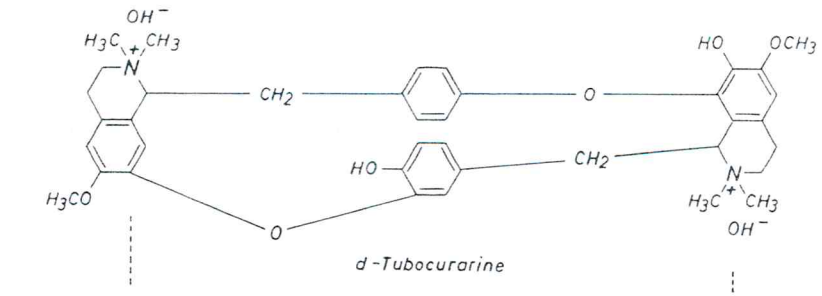
One of these compounds, which has attained therapeutic importance and has the same mechanism of action (competitive inhibition) as *d*-tubocurarine, is called gallamine. It is less potent than *d*-tubocurarine, and therefore the required dose is about five times as high. The effect fades somewhat more readily. Gallamine does not release histamine but may elicit sinus tachycardia.

Some anesthetics have a "curarelike" side effect at the motor end plate. This effect is especially pronounced in ether anesthesia, so that in this case much smaller amounts of *d*-tubocurarine or gallamine are required to produce neuromuscular blockade. "Normal" doses would produce too marked an effect.

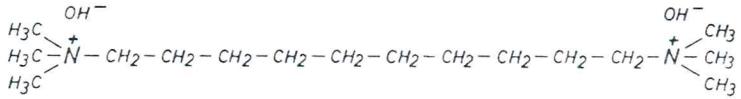
Depolarizing Inhibitors

During the investigation of compounds patterned on the simplified molecular model of *d*-tubocurarine (2 quaternary nitrogen atoms 14 Å apart and 10 intermediate atoms), compounds were found that also reacted with the acetylcholine receptor at the motor end plate but, in contrast to *d*-tubocurarine, did not have a competitive action, but rather like acetylcholine, depolarized the end plate. Since the elimination of these compounds occurs much more slowly than that of acetylcholine, the end plate remains depolarized for a longer period of time and is thereby rendered inexcitable.

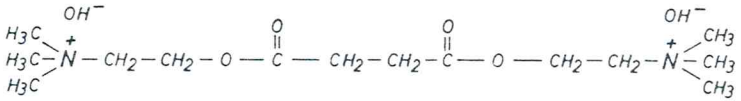
Decamethonium is a very active compound. The intravenous dose for complete muscular paralysis in the adult is 3 mg, i.e., only 20% of the necessary dose of *d*-tubocurarine. The effect lasts for 10–15 min and is not cumulative in ordinary usage as is that of *d*-tubocurarine. As can be expected from the mechanism of action, short-lived muscle fasciculations occur immediately after injection. Neostigmine is not an antidote but enhances the effect of decamethonium. This depolarizing blocker is excreted by the kidney in the unchanged form. With renal insufficiency a more intense and prolonged effect of decamethonium must be expected. Muscles of the



d-Tubocurarine

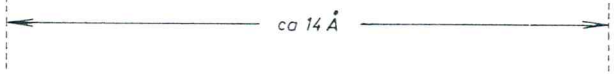


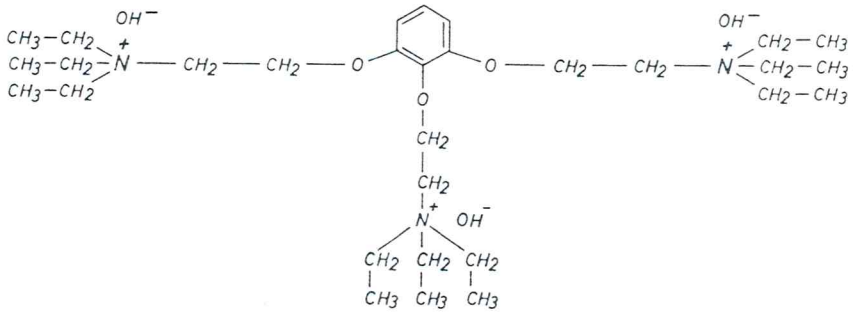
Decamethonium, C_{10}



Succinylcholine

bischoline ester of succinic acid





Gallamine

[v-Phenenyltris(oxyethylene)]-tris[triethylammonium hydroxide]

extremities and the neck are especially sensitive to the drug. The respiratory muscles are last to be paralyzed. Side effects do not occur in therapeutic doses.

Animal experiments indicate that decamethonium has a dual action under certain conditions. The depolarizing action always predominates shortly after administration, and is then followed by a second phase during which it acts as a competitive inhibitor (cf. p. 314).

Succinylcholine has the shortest duration of action of all neuromuscular blocking agents. The effect of a paralyzing dose of 30–150 mg given intravenously disappears after about 10 min, since the drug is hydrolyzed rapidly, both spontaneously and by the nonspecific cholinesterase. An intermediate step in hydrolysis is the formation of the monocholine ester of succinic acid which also has neuromuscular blocking activity. Succinylcholine is especially useful where a very short duration of action is desired (electroshock therapy) and for continuous infusions that can be well controlled.

With regard to the mechanism of action, and its practical consequences (muscular fasciculation and the inactivity of neostigmine as an antidote), it behaves exactly as decamethonium. A frequent but harmless side effect is myalgia, which occurs 1 day after injection and may be present in all muscle groups. The muscular pain may be prevented by pretreatment with *d*-tubocurarine in quantities that do not cause neuromuscular blockade themselves. Very seldom, a marked neuromuscular paralysis of long duration has been observed after normal doses of succinylchóline (acquired or genetically determined cholinesterase deficiency).

Cholinesterase Inhibitors

The mechanism of action of cholinesterase inhibitors has been described on page 13 and page 263. Here the description of the use of these drugs is restricted to the field of neuromuscular transmission.

Cholinesterase inhibitors increase the concentration of acetylcholine at the motor end plate. Such an effect is desired after an overdose of *d*-tubocurarine and in myasthenia gravis. This chronic disease is characterized by diminished neuromuscular transmission. The possible causes are either insufficient liberation of acetylcholine per nerve stimulus or an insufficient sensitivity of the end plate membrane. In either case a decrease in the rate of hydrolysis of the liberated acetylcholine should improve the condition. Indeed, one can observe an increase in muscle strength in patients with myasthenia gravis after administration of cholinesterase inhibitors. In general neostigmine, edrophonium, or the longer-acting pyridostigmine (individual oral dosing) are used. Simultaneous administration of parasympatholytic agents helps to moderate the unpleasant parasympathetic stimulation.

Spinal Cord

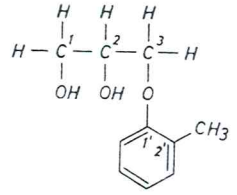
The tonus of skeletal muscle is maintained by polysynaptic reflexes. Thus it can be expected that compounds that stimulate or inhibit polysynaptic reflexes influence the functions of the skeletal musculature. Strychnine is a drug that can markedly

augment the distribution of impulses. Since the effect is not restricted to the spinal cord but can also be demonstrated at higher levels of the central nervous system, strychnine will be discussed as an analeptic (cf. p. 207). In the discussion of strychnine poisoning, it is pointed out that there exist compounds which inhibit the polysynaptic transmission of reflex activity.

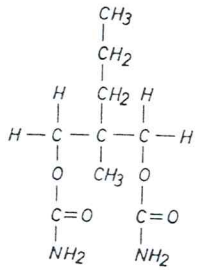
One of these compounds is mephenesin, which was initially introduced as a centrally acting muscle relaxant. The tonus of skeletal muscles is depressed as the result of inhibition of reflexes in the spinal cord; it has no curarelike effect on the musculature itself. The depressive effect of mephenesin is not restricted to the spinal cord but can also be shown to occur in the brain stem, indicating that mephenesin and related compounds can be used as sedatives.

The use of mephenesin for muscle relaxation during anesthesia is no longer practiced because the side effects are too severe. In combination with barbiturates there is a danger of respiratory paralysis. Intravenous administration leads to damage of the venous walls and of erythrocytes so that thrombophlebitis and intravascular hemolysis have to be considered. The dangerous side effects do not occur upon oral administration of small doses in the treatment of spastic conditions, but disturbed vision (nystagmus, double vision) and irritation of the intestinal tract with loss of appetite and vomiting have been observed. The rapid rate of elimination is very disadvantageous in connection with the use of mephenesin as well as guaiacol glycerol ether. The compounds are probably metabolized in the liver; only a small percentage is excreted unchanged. To obtain a sufficiently high blood level, the necessary intravenous doses are in the range of 1–2 gm. In the prolonged treatment of spastic conditions 1–3 gm are given several times daily by mouth.

Meprobamate represents a further development and is used mainly as a tranquilizer. It is discussed in the section on psychotropic drugs (cf. p. 200). The *N*-



Mephenesine
3-o-Tolyloxy-1,2-propanediol



Meprobamate
Carbamic acid 2-Methyl-2-propyltrimethylene ester
An isopropyl group is substituted for an amino hydrogen in carisoprodol

isopropyl derivative of meprobamate, carisoprodol, can be used for the treatment of pathologically elevated tonus of skeletal muscle that occurs with certain spinal or cerebral disorders or as a symptom of rheumatic or other inflammatory diseases. The action of carisoprodol is not restricted to the spinal cord. Drowsiness and decreased reactivity occur as an expression of the inhibition of higher centers. It is contraindicated for car drivers and people operating machinery. A skin reaction may occur as a side effect. A compound with similar indications for use, but apparently lower activity, is chlormezanone, 2-(*p*-chlorophenyl)-3-methyl-1,3-thiazan-4-one-1,1-dioxide. A drug with similar activity but differing chemical structure is phenyramidol [α-(pyridyl-2-aminomethyl)-benzyl alcohol]. An interesting development in this field is drugs from the group of benzodiazepine derivatives, especially diazepam, which apart from their muscle relaxant activity also possess tranquilizing properties (cf. pp. 167, 201).

Extrapyramidal System

Antiparkinsonism Drugs

Classic Parkinsonism is a complex of symptoms caused by cell deterioration within motor nuclei of the brain stem. Tremor and muscular rigidity are the main manifestations. Dopaminergic neurons that commence in the substantia nigra inhibit cholinergic neurons and interneurons. This complex interdependence explains the complicated variety of symptoms and also indicates why a specific pharmacological influence on these manifestations is so difficult. In Parkinsonism the dopamine content of the dopaminergic neurons in the extrapyramidal system is reduced. This may occur in the following ways. (1) In human pathology by the degeneration of some of the storage neurons; (2) after reserpine treatment, because of the inactivation of the storage mechanism in still vital neurons; (3) after administration of chlorpromazine and related drugs or butyrophenones as a result of increased dopamine turnover. The depletion of dopamine results in a disturbance of the equilibrium normally present between the two transmitter compounds of the extrapyramidal system, i.e., acetylcholine and dopamine.

There is essentially no equivalent to Parkinsonism that can be used in animal experiments. Several experimental procedures are designed as models that might allow a certain preselection of agents to be used against Parkinson's disease. Such model experiments are performed in the following manner. Administration of bulbocapnine, harmine, or nicotine initiates muscle tremor; tremorine (1,4-dipyrrolidino-2-butyne), in addition to tremor provokes salivation, miosis, and rigidity. In monkeys it is possible to generate muscle tremor by surgery in the mesencephalon. The above-mentioned symptoms are improved by antiparkinsonian drugs.

For therapeutic purposes, it seems useful to elevate the depressed dopamine content by administration of L-dopa. (Dopamine, in contrast to its precursor, does not penetrate into the brain.) Oral therapy (3–4, up to 8 gm daily) may be surprisingly successful. Nevertheless, such treatment is symptomatic and not com-

pletely satisfactory, particularly since it is only effective against the akinesia and rigidity. Dopa is well absorbed from the intestine and rapidly excreted via the kidney as metabolites. Side effects are frequent, especially after higher doses. Apart from nausea and vomiting, dyskinetic states often dominate. Psychotic manifestations are rare. Occasionally autonomic disturbances such as orthostatic hypotension are observed. The side effects, but also the therapeutic effect are abolished by the administration of pyridoxine.

In order to depress the tone of the cholinergic system which predominates in Parkinsonism, the alkaloids scopolamine and atropine must be given in rather high dosage (up to 5–20 mg daily).

Severe side effects occur via the peripheral autonomic nervous system (inhibition of salivation, paralysis of accommodation, etc.) which are only slightly improved by the administration of parasympathomimetics such as neostigmine. The complete extract from belladona root ("Bulgarian cure") is said to be more effective than the pure alkaloids. Apart from the parasympatholytic alkaloids (atropine, scopolamine), a number of synthetic drugs are available for attempts at therapy. The responsiveness of the individual patient to particular drugs is exceedingly varied, so that frequently only by trial and error can the most favorable medication be found. Each course of treatment must be started with very small quantities of the drug, which are then slowly increased until the desired effect occurs or the side effects become too pronounced. Even though a drastic improvement in the clinical picture cannot usually be obtained, diminished symptomatology is frequently achieved.

Besides the alkaloids, there are some synthetic compounds that have proved to be of use in some cases. Trihexyphenidyl (3-[1′-piperidyl]-1-phenyl-1-cyclohexyl-propanol-1), the closely related compound, biperiden (3-[1′-piperidyl]-1-phenyl-1-bicycloheptenyl-propanol-1) or caramiphen (1-phenyl-cyclopentane-1-carbonic acid-β-diethyl-aminoethyl ester) should be considered in cases of rigidity, while ethopropazine (10-[2′-diethylaminopropyl-1′]-phenothiazine) and possibly trihexyphenidyl are reported to be especially effective against tremor. The side effects of this group of compounds—mainly inhibition of the parasympathetic system and a central nervous system impairment—are not serious but rather unpleasant and may preclude treatment with sufficiently high doses. Ethopropazine is a close chemical relative of promethazine and chlorpromazine (cf. p. 193).

Amantadine, originally introduced as a virostatic agent (formula and side effects, p. 299) may produce subjective improvement in many patients. Objectively, the rigidity and tremor may improve but not always the akinesia.

A combined therapy, taking into account both the dopaminergic and the cholinolytic components is frequently useful, especially since in this manner the side effects may be moderated. This also holds true for the combination of dopa with amantadine. Sometimes central stimulants such as caffeine or methamphetamine result in favorable therapeutic effects.

CHAPTER 3

SENSORY SYSTEM

Peripheral Nervous System

Local Anesthetics

The term local anesthesia is understood to mean a reversible loss of sensitivity to pain in a restricted area. Correspondingly, local anesthetics are drugs which transiently inhibit the sensation of pain. The locus of action of these substances, which are always applied to a restricted area, is the afferent nerves and sensory end organs. Local anesthetics are not general anesthetics which influence the function of the brain and thereby the perception of pain. When local anesthetics are distributed throughout the whole organism they are rather toxic; hence, systemic absorption must definitely be avoided.

The following is known about the mechanism of action of local anesthetics. The conduction of a nerve impulse is expressed as an action potential which is propagated along the cell membrane. This electrical excitation results, in this case, as in the muscle cell, from a change in cation permeability. The rise of the action potential, i.e., depolarization, is accompanied by a sudden, marked increase in sodium permeability which is followed by a flow of sodium ions into the cell in accordance with the existing gradient. A similar process presumably occurs in the sensory end organ to initiate the impulse. Local anesthetics diminish this sodium influx. This results in decreased excitability, which can lead to a complete loss of excitability. It can be shown experimentally that such a block may be counteracted by the application of catelectrotonus (see the scheme in Fig. 43).

The molecule of a typical local anesthetic contains a tertiary amine that is present

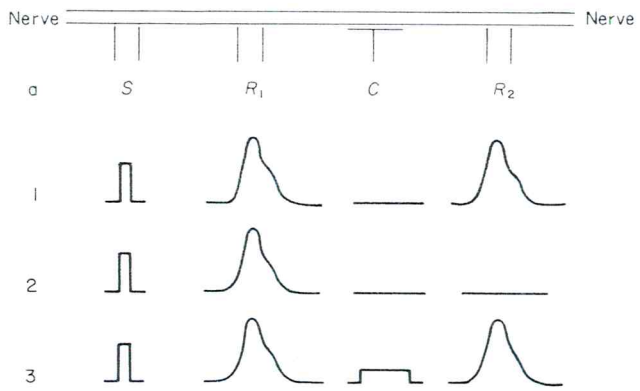
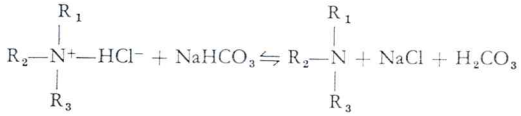
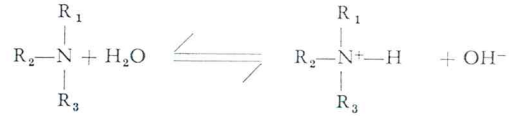


Fig. 43. Schematic representation of an experiment in which nerve conduction is blocked with a local anesthetic and restored with cathodic polarization. In (a) the experimental conditions are shown: S, stimulating electrodes; R_1 and R_2, recording electrodes; C, site of local anesthetic application and also of the electrode for cathodic polarization. Experiment 1 is the control; the stimulus elicits a propagated response which is measured by both recording electrodes. Experiment 2 was carried out after the application of a local anesthetic at C. The stimulus elicits a propagated response which is only recorded by the electrode pair R_1 since the nerve has become unexcitable between R_1 and R_2 and therefore the response does not reach R_2. In experiment 3 following induction of blockade by the local anesthetic, and stimulation of the nerve at S, a cathodic impulse has been applied by electrode C. Now the stimulus is propagated through the previously inexcitable area and is recorded by electrode R_2. The effect of a local anesthetic can be abolished by catelectrotonus.

as a salt in the usual commercial solutions and which is converted into the free base at physiological pH values.



Only the free base is capable of penetrating tissue barriers. However, the reaction with biological structures appears to occur mainly with the cationic form with its quaternary nitrogen atom.



The effectiveness of a local anesthetic is particularly dependent on the proportion of free base formed in the tissue, which in turn is determined by the pH of the environment and on the pK value of the compound in question. The more alkaline the tissue, the more free base is present and vice versa. Since inflamed tissue has

a more acidic pH, the diminished activity of local anesthetics in such conditions is explicable. At the actual site of action (the cell membrane) the reaction probably occurs with the tetravalent (charged) form (Fig. 44); this is analogous to other quaternary nitrogen compounds (acetylcholine, neuromuscular, and ganglionic blocking agents) that also have pronounced effects at the cell membrane.

Starting with cocaine, a remarkable number of substances with local anesthetic activity have been synthesized since the turn of the century. In practice only a few agents are quite sufficient. Common to all is a certain molecular arrangement that is present even if the compounds belong to quite different chemical classes (see the structural formulas). The necessary groups are (1) the tertiary

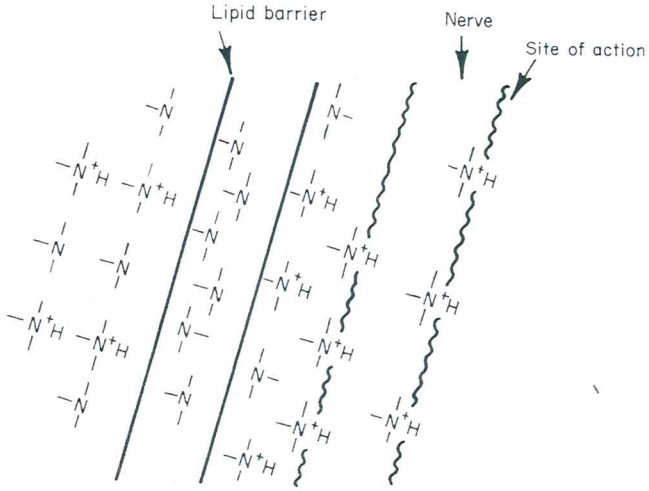


Fig. 44. Schematic representation of the penetration of the local anesthetic through tissue barriers to its site of action. The direction of diffusion is from left to right.

amine and (2) the polar carbonyl oxygen atom that can belong to an ester or an amide group. The distance between the two active centers is 2–4 atoms. The remainder of the molecule is of little importance to the actual local anesthetic activity but strongly influences the physicochemical properties such as solubility, rate of diffusion, the dependence on pH for the formation of the free base, and the liability to be degraded in the tissue. There are a great number of available local anesthetics which, however, do not possess any advantages over those compounds listed below.

In local anesthesia three modes of application should be differentiated:

1. Surface anesthesia of mucous membrane and wounds. The agent is applied to the surface and diffuses to the sensory receptors and the fine branches of the sensory nerves.

2. Conduction anesthesia. The anesthetic is applied to the nerve trunk and

blocks conduction in the afferent nerves. Spinal anesthesia and its modifications are special cases of conduction anesthesia. Since lumbar anesthesia is a greater risk than general anesthesia in the hands of the inexperienced, the former procedure should only be chosen in cases where indications for its use are obvious. Special preparations of the local anesthetics are usually employed in lumbar anesthesia in order to prevent rapid upward diffusion from the site of injection in the spinal fluid, since dangerous complications arise if the local anesthetic reaches centers in the medulla oblongata.

3. Infiltration anesthesia. The local anesthetic is injected into the tissue, where it is distributed and reaches the sensory end organs and the fine branches of the afferent nerves.

Local anesthetics do not specifically block the sensory nerves; motor nerves may also lose their ability to conduct. However, the sensitivity of individual nerve fibers is correlated with their diameter. Since the sensory fibers are smaller than the motor fibers, the former are the first to be blocked. The concentration of local anesthetics is always chosen so as to be just sufficient to paralyze the afferent fibers.

Some local anesthetics have vasodilator activity, e.g., the hydrolysis of procaine liberates a compound with vasodilatory properties, i.e., diethylaminoethanol. The local anesthetics therefore are mixed with a vasoconstrictor compound. The reasons for this procedure are (1) surgical intervention in the anesthetized region is easier with diminished blood flow and (2) the local anesthetic may be removed too rapidly if the blood flow is marked. This shortens the duration of action and increases the systemic toxicity. The added vasoconstrictor is usually epinephrine or norepinephrine. The dose of the additives has to be kept within very exact limits since catecholamines are extremely potent and after absorption can be toxic. The total amount of epinephrine or norepinephrine must not exceed 0.25 mg (corresponding to about 5 drops of a 1:1000 solution) for a single application of a local anesthetic, regardless of whether 2 ml of a 2% procaine solution are injected for conduction anesthesia or 100 ml of 0.5% procaine solution are given for infiltration anesthesia.

Local anesthetics have the following side effects, which may lead to serious complications:

1. An inhibition of the heart, which can occur when an excessive concentration of the drug in the heart is reached by too high a rate of absorption or through accidental intravenous injection. As in nerve, primarily the conduction of impulses is inhibited. Total atrioventricular block with ventricular arrest may occur which leads to death of the patient within a few minutes as a result of central anoxia (perhaps accompanied by anoxic convulsions). The treatment must consist of stimulation of cardiac activity within the first minute. The drugs which stimulate the heart to the greatest extent are epinephrine and isoproterenol (Fig. 45). Intracardiac injections are required in these circumstances. In addition, cardiac massage should be undertaken so that the drugs are forced out of the cardiac lumen into the coronary circulation, and accordingly reach the pacemaker cells, conduction system, and myocardial cells.

2. An "excitatory" effect on the central nervous system, which is initiated by a blockade of inhibitory neurons. This effect depends mainly on the total amount

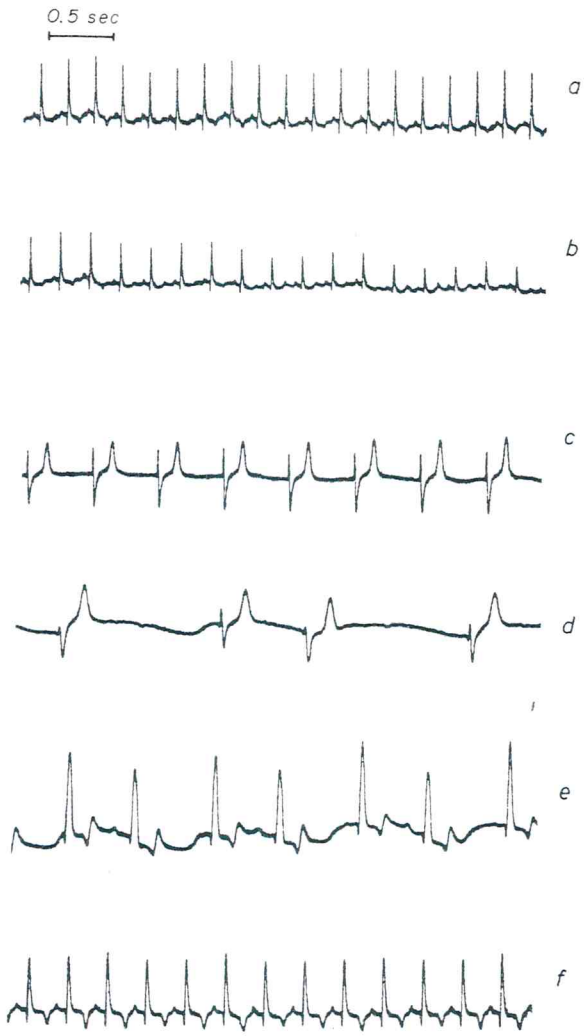


Fig. 45. The EKG of an anesthetized guinea pig. Intravenous infusion of tetracaine (20 mg/kg). Subsequent injection of epinephrine (0.3 mg/kg). (a) EKG prior to tetracaine infusion; (b–d) During the infusion of tetracaine. (e and f) Immediately and 2 min after epinephrine injection. Note the marked alleviation of tetracaine toxicity.

of the local anesthetic absorbed. Slight symptoms are restlessness, tremor, and nervous anxiety. In serious cases clonic convulsions occur that make respiratory movements impossible. The condition presents the danger of central anoxia. Following the clonic convulsions the respiratory center may be paralyzed. The treat-

ment of this convulsive condition consists in the intravenous (or if this is not possible, intraperitoneal) injection of a rapidly acting depressant (hexobarbital appears to be best). Artificial respiration can and must be given until the intoxication has disappeared (this takes only a relatively short time).

The cases of poisoning described under 1 and 2 above may appear similar in their symptoms (fainting, cyanosis, and convulsions) but they require completely different treatment. Therefore, a differential diagnosis must be made immediately on the basis of cardiac activity.

3. Allergic reactions may occur that vary in intensity from a slight skin reaction to anaphylactic shock. It should be pointed out here that procaine is contained in some penicillin depot preparations (cf. p. 276). The treatment of such allergic reactions is independent of the agent which precipitates them.

4. With overdosage of the added vasoconstrictor amine, the heart may become hyperexcitable. Depending on the severity of the condition, this manifests itself as tachycardia, extrasystoles, and finally as ventricular fibrillation (cf. p. 19).

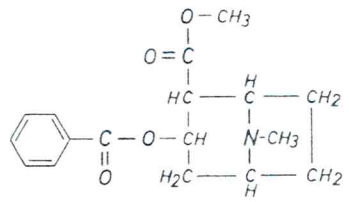
Procaine is one of the oldest and most frequently used injectable local anesthetics. Since it is hydrolyzed quickly in the tissues by esterases, it is relatively nontoxic and short acting. For the same reason it cannot be used as a topical anesthetic (improper ratio between the rate of diffusion and that of degradation). Depending on the intended use, solutions contain between 0.5 and 2% of the drug.

Lidocaine acts more quickly than procaine and its degradation is slower. As a result of these properties, it has a longer duration of action than procaine and may be used as a surface anesthetic. Depending on the intended use, solutions contain between 0.25 and 1.0% (solutions of 2% should be avoided). The total amount of lidocaine should not exceed 0.5 gm within a day if epinephrine has been added; otherwise it is 0.2 gm.

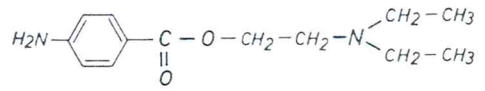
Mepivacaine resembles lidocaine, but its action is more sustained. It is used for conduction and infiltration anesthesia. Addition of a vasoconstrictor is usually not necessary so that mepivacaine is suited to all cases in which the presence of epinephrine presents a hazard. A closely related drug is bupivacaine (the *N*-methyl group has been replaced by a butyl moiety); it acts even longer than mepivacaine.

Tetracaine is about ten times as potent as procaine. It is a very effective topical anesthetic, and should only be used as such because of its higher toxicity. Enzymic hydrolysis of tetracaine is considerably slower than that of procaine; the butyl group may provide steric hindrance to attack by esterases. Consequently the duration of action is relatively long (2–4 hr). It should always be used with the addition of a catecholamine. The maximal dose is 20 mg. Concentrations of 0.1–1% are required for topical anesthesia; if a 2% solution is used, the maximal dose is achieved with 1 ml.

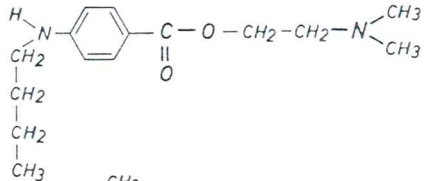
Ethyl *p*-aminobenzoate (benzocaine) is practically insoluble in water, but as a result of its lipid solubility, it penetrates into the peripheral sensory system on long-lasting contact with mucous membranes or wound surfaces. It generates a long-lasting, local anesthesia. Poisoning from systemic absorption is rare but allergic responses are more frequent. Large wounds may absorb quantities that result in methemoglobinemia, since the drug is an aniline derivative. Infants are



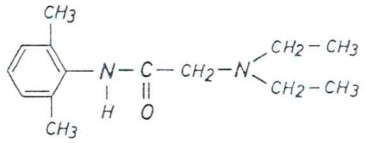
Cocaine
1-Benzoylecgoninemethyl ester



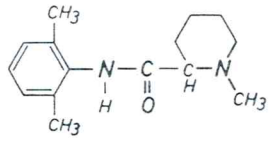
Procaine
2-Dimethylaminoethyl-p-aminobenzoate



Tetracaine
2-(Dimethylaminoethyl) ester of p-butylaminobenzoic acid



Lidocaine
2-Diethylamino-2',6'-acetoxylidide



Mepivacaine
1-Methyl-2',6'-pipecoloxylidide

especially susceptible. Ethyl *p*-aminobenzoate is used in various preparations of 5–20%.

Cocaine occurs in the leaves of South American species of *Erythroxylon*. The leaves are chewed by natives in Peru and Bolivia for their stimulatory effects. In addition to its local anesthetic effect, cocaine has a number of other properties that result in a rather complicated symptomatic picture. As a surface anesthetic it has only one-fifth to one-tenth the activity of tetracaine. In contrast to the synthetic local anesthetics, cocaine has a vasoconstrictor effect, which must be attributed to its action in sensitizing adrenergically innervated tissues to epinephrine, (cf. p. 29). Since cocaine has a sympathomimetic effect on other organs, such as the

heart, addition of epinephrine to its solutions is not only unnecessary but increases toxicity. With absorptive poisoning, even 50 mg of cocaine is often sufficient to precipitate a life-threatening condition. Along with the symptoms of increased sympathetic excitation, the function of the central nervous system is affected in acute cocaine poisoning, initially appearing as excitation followed by a depression of cerebral function. Death follows after epileptiform convulsions and is caused by central respiratory depression. In acute poisoning a rapidly acting barbiturate (e.g., hexobarbital) must be injected immediately and artificial respiration started. Slight intoxication of the brain with cocaine may cause symptoms in certain people that give rise to a psychic dependency on the drug: euphoria, pleasant hallucinations, a feeling of greater performance, etc. The drug is usually taken as snuff in such circumstances.

As a result of its acute toxicity and psychic effects, cocaine has been replaced by synthetic local anesthetics. An exception may be its use in the eye, if mydriasis is required at the same time as anesthesia (several drops of a 5% cocaine solution; maximal dose 50 mg).

Central Nervous System

Analgesics, Antipyretics, Antirheumatics

The substances included in this chapter have to a varying extent analgesic, antipyretic, or antirheumatic properties. Depending on the reason for their use, one or the other of these qualities predominates; the other effects are then desirable (or undesirable) side effects. Inhibition of the perception of pain is localized in the central nervous system. Whether this inhibition is a cortical or subcortical process has not yet been clearly determined. The analgesic potency of this group of drugs is less than that found in the opiates, but they are free from narcotic, euphoric, and addictive side effects. The antipyretic effect is also based on a central activity. The ratio between heat production and heat dissipation, which is abnormal during fever, is affected by antipyretics through an influence on the hypothalamic centers that regulate the body temperature. The temperature is normalized as the result of increased cutaneous circulation and sweating. The normal temperature of the body or that associated with hyperthermia (e.g., produced by overheating or 2,4-dinitrophenol) is not influenced by therapeutic doses of these drugs. The mechanism of the antiphlogistic (antiinflammatory) and the closely related antirheumatic effect of this group of compounds has not yet been satisfactorily explained. Local sites of action are probably involved. There exist arguments in favor of the view that intensive, defensive reactions of the body like fever, pain, and inflammation are suppressed by these drugs at the cellular level, as has been demonstrated for the salicylates.

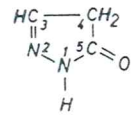
Compounds that have been introduced into therapy belong to different chemical groups—derivatives of pyrazolon, indole, salicylic acid, and *p*-aminophenol.

Pyrazolon Derivatives

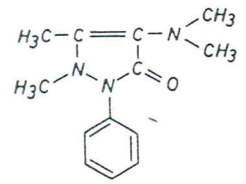
Aminopyrine

Aminopyrine has good analgesic, antipyretic, and antirheumatic properties. The single dose for an adult is in the range of 0.3–0.5 gm, by mouth (or rectally). It is well absorbed from the gastrointestinal tract, the maximal effect being reached after 1 hr. The plasma concentration drops by about 20% per hour. Aminopyrine is metabolized in the liver; one of the first steps is *N*-demethylation, yielding 4-amino-1-phenyl-2,3-dimethyl-5-pyrazolone, a therapeutically active drug like aminopyrine. The demethylated compound is excreted as its *N*-acetyl derivative and represents the main metabolic degradation product (35%) after aminopyrine administration.

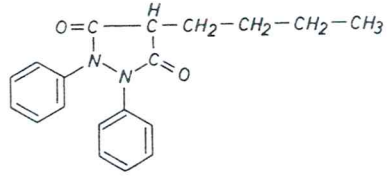
Aminopyrine and compounds related to it are very frequently used without justification. When related to its large consumption, side effects very seldom occur. Allergic skin reactions and occasionally leukopenia and lethal agranulocytosis resulting from an allergic reaction occur (cf. General Considerations on Side Effects p. 331). The number of lethal cases of agranulocytosis is probably much higher than generally accepted so far. In very high doses aminopyrine is a convulsant. The oral lethal dose in man is about 10 gm.



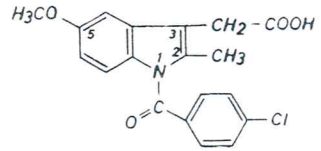
5-Pyrazolone



Aminopyrine
4-Dimethylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one



Phenylbutazone
4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione



Indomethacin
1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

At neutral pH aminopyrine is poorly soluble. Modification by introduction of a methanesulfonyl group into the 4-amino residue produces a more soluble product. The compound novaminsulfone (the salt of 1-phenyl-2,3-dimethyl-4-methylamino-

pyrazolone-5-*N*-methanesulfonic acid) has been introduced into therapeutics as an injectable preparation. Another possibility for dissolving aminopyrine sufficiently in order to make an injectable solution is to form a mixture with phenylbutazone. Since phenylbutazone has specific effects, the actions and side effects of this combination are mainly determined by phenylbutazone.

Phenylbutazone

Orally administered phenylbutazone is absorbed nearly completely. The substance is metabolized more slowly than aminopyrine because its strong binding to plasma proteins interferes with its degradation. Consequently, phenylbutazone accumulates in the body. On the basis of this accumulation and of side effects, the daily dose must not exceed 0.6 gm during the first days of administration and 0.4 gm thereafter. The time during which the drug is used should be limited as much as possible. Patients taking phenylbutazone should be under the care of a physician, so that the blood picture, the occurrence of occult blood in the feces, body weight, and urine analysis can be checked.

Side effects are considerably more frequent with phenylbutazone than with aminopyrine or other analgesics. About one third of all patients exhibit side effects; in 10% of the cases therapy must be discontinued because of intolerance to the drug. Apart from an abnormal blood picture (leukopenia, agranulocytosis), there are the toxic side effects on the intestinal tract (upper abdominal pain, damage to mucous membranes with bleeding, reactivation of old ulcers) and the kidney (water and salt retention with a noticeable increase in weight of the patient and sometimes acute renal failure). These are especially serious. Even the occurrence of acute leukemia has been reported. The intramuscular injection of phenylbutazone-aminopyrine combinations can lead to local tissue damage (perhaps ischialgic complaints). As a result of these side effects, the therapeutic risk must be considered very carefully before the compound is prescribed.

The indications for phenylbutazone must be differentiated from those of aminopyrine. While the latter may be used equally well for all three indications (analgesic, antirheumatic, and antipyretic), phenylbutazone is employed, if at all, in gout. Similarly, pain (such as toothaches or menstrual difficulties) is no indication for phenylbutazone.

The metabolic products of phenylbutazone such as oxyphenbutazone and related compounds such as nifenazone are not to be distinguished in their activity or side effects, despite contrary reports. Because of their small therapeutic index, they are not suited for routine prescription as an antirheumatic or analgesic.

Indole Derivatives

Indomethacin acts primarily as an antirheumatic and for this reason is employed in acute and chronic polyarthritis and other chronic rheumatic diseases. Its potency is comparable to that of acetylsalicylic acid. In actual attacks of gout it is as effective as phenylbutazone. The daily oral dose is in the range between 75 and 200 mg. The side effects of indomethacin and phenylbutazone are very similar: gastrointestinal disorders, eventually ulcers, edema, hepatic damage, bronchial asthma;

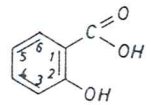
in addition there is an impairment of vigilance, disturbances of the sensorium, and possibly the activation of latent infections. The drug should be given to children only with extreme caution.

Salicylic Acid Group

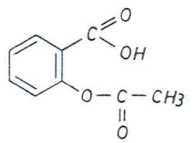
Salicylic acid is absorbed by the intact skin. After oral administration it irritates the gastric mucosa; localized point-bleeding may occur. Because of the poor oral tolerance to salicylic acid, acetylsalicylic acid is preferred generally. The antirheumatic properties of both drugs are approximately equivalent. The analgesic and antipyretic properties are more pronounced with acetylsalicylic acid.

Acetylsalicylic Acid (Aspirin)

Acetylsalicylic acid also irritates the gastric mucosa, and should not be taken on an empty stomach. Absorption from the intestinal tract is rapid and complete. To achieve proper blood levels (about 30 mg/100 ml) in rheumatic fever, the adult patient must take 6–10 gm distributed over 1 day. Excretion occurs quickly through the kidney as salicylic acid, conjugated to a varying extent, depending on the pH of the urine, with glycine and glucuronic acid. Only a very small proportion is oxidized to gentisic acid.



Salicylic acid
o-Hydroxybenzoic acid



Acetylsalicylic acid
Aspirin

While the indications for salicylic acid or its sodium salt are mainly restricted to rheumatic diseases, acetylsalicylic acid can be used additionally very effectively for the treatment of pain or fever in daily, oral doses of 1.5–5 gm.

The inclination of thrombocytes to form aggregates is inhibited by acetylsalicylic acid in rather low dosage. This effect may be used in the prophylaxis of thrombosis.

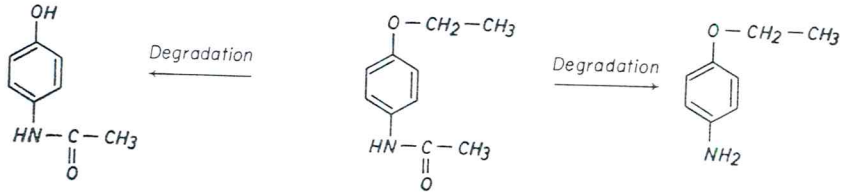
Since acetylsalicylic acid or salicylic acid is given over long periods of time in high doses in order to treat rheumatic diseases, there are a number of side effects originating in the central nervous system that occur quite frequently: ringing in the ears (tinnitus) with dizziness, hearing difficulties, headaches, and numbness. These symptoms disappear with a reduction of the dose. Allergic reactions (urticaria, asthma) are very rare. During treatment with acetylsalicylic acid the prothrombin level drops (vitamin K has an antagonistic effect). Bleeding has also been observed in the fetus. Gastric tolerance is poor. The formation and composition of gastric mucus is affected since salicylates inhibit the synthesis of mucopolysaccharides. The mucosa can be so severely damaged that bleeding results. Microscopic sites of hemorrhage are almost always demonstrable.

The principal disturbance that occurs in *poisoning* with salicylic or acetylsalicylic acid involves the acid-base balance of the blood. The carbon dioxide tension and the bicarbonate concentration fall, owing to marked hyperpnea of central origin; the urine becomes alkaline; and the blood pH is either unchanged or slightly shifted toward the alkaline side. Finally, following a period of excitation, unconsciousness, dyspnea and death as a result of paralysis of the respiratory center occur. Therapy for intoxication must produce a rapid normalization of the disturbances in acid–base and electrolyte balance. As soon as the respiratory alkalosis has been abolished by the addition of CO_2 to the inspired air, sodium bicarbonate or lactate must be given (while respiration is watched closely) since the excretion of salicylates is thereby considerably increased. The administration of mannitol solutions is also useful in such therapy. In extreme cases of poisoning, the life of the patient may be saved by exchange transfusions and peritoneal dialysis.

p-Aminophenol Derivatives

Phenacetin, Acetaminophen

These compounds are very good analgesics and antipyretics. The antirheumatic effects are less pronounced. The adult oral dose is about 0.25–0.50 gm two to three times daily. Phenacetin is absorbed quickly and completely and is converted in the body into acetaminophen, which in turn has an analgesic and antipyretic action. Only a small part of the phenacetin is converted into *p*-phenetidin, which, being an aniline derivative, causes formation of methemoglobin. This reaction may be neglected in adults after usual doses. The methemoglobin level, however, may reach high levels much more easily in infants. For this reason acetaminophen should be substituted for phenacetin with infants and small children, since methemoglobin formation after administration of the former drug is negligible. Phenacetin and acetaminophen have virtually no acute side effects in adults when given in therapeutic doses. Currently acetaminophen can be regarded as probably the best simple analgesic.



Acetaminophen
N-acetyl-p-aminophenol

Phenacetin
p-Ethoxyacetanilide

p-Phenetidin

Chronic administration of excessive doses of phenacetin alone is not usual. However, its chronic use in combination with caffeine, codeine, or hypnotics is frequent. Following long-lasting treatment with such mixtures the following symptoms of

poisoning may occur—anemia, cyanosis, headaches, psychic disturbances, interstitial nephritis, and renal papillary necrosis. Lipofuscin accumulations are found in the liver. It inadvisable, if prolonged treatment with analgesic drugs is necessary, to administer the same drug (as a pure compound or in mixtures) over long periods of time. A regular change between drugs from various chemical groups is to be preferred. Similarly, already existing renal damage requires cautious prescription of analgesics. Phenacetin should also be avoided when anemia is present since it significantly shortens the life span of erythrocytes.

Antineuralgic Combination Preparations

Analgesics are frequently combined with each other and with other drugs and offered commercially as pain relievers. The components are hypnotics (usually barbiturates), stimulants such as caffeine or both together, and codeine. In general these mixed preparations are present in every medicine chest and are taken too frequently and without cause. When used sensibly and in moderate doses, toxicity appears to be rare (concerning chronic abuse see the previous paragraph). Preparations that contain hypnotics and caffeine may lead to habituation with extended use.

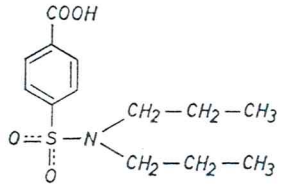
Drugs Used in the Therapy of Gout

The treatment of an acute attack of gout should be distinguished from long-lasting prophylaxis in cases of elevated uric acid levels.

The symptoms of an acute attack usually can be relieved by the administration of colchicine. Colchicine is an inhibitor of mitosis (cf. tumor chemotherapy, p. 308). The mechanism of action by which it exerts a favorable effect in gout has not yet been elucidated. Colchicine has no analgesic properties; neither does it lower the uric acid level in the blood, nor promote the renal excretion of uric acid. The dosage is about 1 mg several times daily. The first symptom of toxicity which may occur with usual doses is diarrhea. Poisoning with higher doses resembles that caused by arsenic. An acute attack of gout can also be treated with phenylbutazone; since in this case it is given for only a short time, side effects are to be feared less than upon prolonged administration. Indomethacin is as efficacious as phenylbutazone. Supplementary administration of glucocorticoids or corticotropin frequently is of value.

In chronic gout the goal of any therapy should be an improvement in the uric acid balance. Probenicid has been found particularly useful for this purpose. It inhibits the reabsorption of uric acid in the renal tubule, resulting in a greater excretion of the uric acid contained in the glomerular filtrate (uricosuric effect). The blood level of uric acid drops, and thereby the frequency of attacks. New tophi are no longer formed, and those existing may eventually disappear. Sulfinpyrazone {1,2-diphenyl-4-[2′(phenylsulfinyl)ethyl]-3,5-pyrozolidinedione} has a similar effect, but gastrointestinal disturbances may occur. Allopurinol has a different mechanism of action by inhibiting xanthine oxidase (cf. p. 307). The formation of uric

acid is reduced and its blood level falls. Accordingly, xanthine and hypoxanthine, the precursors of uric acid, could accumulate but do not since they are excreted via the kidney much more easily than is uric acid itself. This therapy appears to achieve the best results, particularly when renal function is simultaneously impaired.



Probenecid
p-(Dipropylsulfamoyl) benzoic acid

Therapy of Rheumatic Diseases

Acute as well as chronic rheumatic conditions are subject only to symptomatic treatment. Nevertheless, the success of such treatment can be outstanding as far as the lessening of pain and functional disturbances are concerned. In chronic rheumatoid diseases withdrawal of the medication usually also means a recurrence of the initial complaints. For the treatment of such diseases several classes of compounds are available—(1) pyrazolon derivatives, (2) salicylates, (3) indole derivatives, and (4) glucocorticoids. These agents must be considered essentially equivalent with regard to the results that may be achieved. Each of these groups has different side effects, some of which may be dangerous. With the appearance of marked side effects, a change from a drug of one group to a drug of another class may be indicated. Combinations of an agent from groups 1, 2, or 3 with a compound from group 4 leads to an additive therapeutic effect and diminished side effects. All daily doses are given equally distributed over 24 hr. Aminopyrine is given in acute rheumatic fever orally or rectally in doses of 2–4 gm. Phenylbutazone, if required at all, is given in doses of 0.6 gm the first day and then 0.2 gm daily. The dose of phenylbutazone must be reduced very quickly because of this drug's great tendency to accumulate. It is not clear whether or not penicillin given in the initial stage of rheumatic fever can affect the acute phase, but it is reasonable to consider such therapy as the initial step in prophylactic treatment of recurrence (cf. p. 281).

Among the salicylates, acetylsalicylic acid is the drug to be preferred in daily oral doses of 8–10 gm. That dose level should be reduced soon after beginning therapy. In addition, vitamin K_1 is given in a dose of 1 mg/gm of salicylate in order to maintain normal production of prothrombin. Of the glucocorticoids, prednisone, for example, is given in daily oral doses of 30–50 mg initially. The dose level should be reduced promptly.

In chronic rheumatoid diseases, basically the same compounds are active as those given for acute rheumatic fever. Since the treatment is only symptomatic, one should attempt to control the disease with the smallest possible dose in order to minimize the side effects. Combining preparations from the different groups (see above) or alternating periods of use with preparations from different groups

from time to time is very sensible in order to avoid chronic damage resulting from these drugs.

In chronic rheumatoid arthritis and also in chronic discoides lupus erythematosus, treatment with the antimalarial agent, chloroquine, can be attempted. It appears to be effective symptomatically in an unexplained way in many cases after administration of 250 mg daily for a period of months. Subjectively, the favorable effect appears after several weeks; objectively, after at least 2 months. After the glucocorticoids have failed, chloroquine is also only rarely effective. About 10% of all patients do not tolerate the treatment. Numerous side effects can be observed, such as exanthema of the skin, pigmentation, photosensitization, loss of hair, graying of hair, and even epileptiform convulsions. Occasional disturbances of accommodation are observed in the eye, as well as clouding of the cornea as a result of the deposition of crystals, resulting in more or less pronounced visual disturbances. In rare cases after long periods of treatment, damage to the retina in the form of a retinitis pigmentosa may occur. The corneal changes are reversible and even the retinal damage may regress. Central vision is affected last of all. Since the disease can progress after discontinuance of the medication, the daily dose level and the length of the therapy should be as limited as possible. Precise testing of visual function is necessary.

Only in primary chronic rheumatoid arthritis, especially in early cases with little change in the joints, are gold compounds effective in special cases; even long-lasting remissions are obtained. A preparation suitable for intramuscular injection is aurothioglucose. The considerable danger involved in gold therapy has been lessened by the possibility of administering dimercaprol (BAL) if gold poisoning develops. The mechanism of action of gold compounds is unknown. It is speculated that a nonspecific stimulating effect is involved, as in the case of sulfur, which is still sometimes given intramuscularly for similar indications but with less success.

A further possibility for the treatment of rheumatoid arthritis is the use of immunosuppressive agents (cf. p. 301).

The local treatment of rheumatic diseases by rubbing with agents producing hyperemia results in a subjective lessening of the pain.

Pyrogens

Pyrogens, which consist of specific bacterial proteins or lipopolysaccharides, raise the body temperature and act as vasodilators. The vasodilatation is generated centrally. Also, endogenous compounds influence the central regulation of temperature. Etiocholanolone, a metabolite of testosterone, and other steroids with the 3α-hydroxyl-5β- configuration have pyrogenic activity. They might be responsible for fevers of unknown origin and possibly for the temperature elevation during ovulation. In animals, the application of epinephrine to certain areas of the brain lowers the temperature, whereas that of 5-hydroxytryptamine and of some prostaglandins raises it. In peripheral vascular disturbances small doses of pyrogens can be used to raise the temperature moderately (1–1.5°C)—and thereby augment, at least transiently, peripheral blood flow.

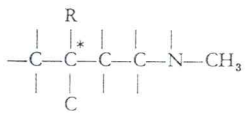
Opiates

The term opiate is limited to pharmacological agents that are comparable in their actions to the principal alkaloid of opium, morphine. They can be natural products such as morphine or partially or fully synthetic. Opium alkaloids that have no pharmacological relationship to morphine, such as papaverine, do not fall under the term opiate.

Opium Alkaloids

The dried juice of the poppy capsule (the fruit of *Papaver somniferum*) contains various alkaloids. The approximate content of the most important is morphine, 10%; narcotine, 6%; papaverine, 0.8%; codeine, 0.5%; narceine, 0.3%, and thebaine, 0.2%. Powdered opium (USP) contains not less than 10% and not more than 10.5% morphine; opium tincture (USP), between 0.95 and 1.05 gm of morphine per 100 ml.

The chemical structure of morphine exhibits a phenanthrene skeleton to which a piperidine and a tetrahydrofuran ring are attached. On the other hand, one may consider the structure as that of a partly hydrogenated isoquinoline ring system. Notably, morphine and related compounds contain the following common structure:



The carbon atom with the asterisk is a center of asymmetry. Most derivatives of morphine having a central analgesic effect possess this structural arrangement. This structure (a tertiary nitrogen atom, two carbon atoms removed from the asymmetric carbon) is shown in boldface type in the formulas. The phenolic OH group appears to be also responsible for the activity. Alkylation, as in methylmorphine (codeine) and ethylmorphine, decreases the analgesic potency and the addictive properties. If the OH group is esterified (e.g., acetylmorphine), the morphinelike activity is enhanced. The analgesic and addictive properties are increased even further, when not only the phenolic but also the alcoholic hydroxyl group is acetylated (diacetylmorphine, heroin). Like most other alkaloids, morphine is hardly soluble as the free base but is soluble as a salt. Recently, compounds such as fentanyl have been synthesized which have morphinelike activity, but no longer chemically resemble morphine. They have strong analgesic activity and are used only in neuroleptoanalgesia.

Morphine

The principal action of morphine is an analgesic effect on the sensory areas of the cortex and possibly on centers in the diencephalon. The actual mechanism that inhibits the perception of pain is unknown. The repression of pain perception is quite specific however. The perception of other modalities in the sensory system is not affected after the administration of a usual dose (10 mg per adult). On the other

hand, even this dose leads to a hypnotic effect in most cases, combined with a depression of the mental activity of the patient. Higher doses generate an anesthesia-like condition with loss of consciousness. One characteristic feature of morphine is the changed mood of the patient after therapeutic doses: feelings of depression and anxiety are lifted and everything is seen in a rosy light, i.e., the patient becomes euphoric. This euphoric state occurs much more rarely in persons in a normal state of mind. Pronounced dysphoria is more frequent. Sometimes conditions of unrest, excitement, and uncoordinated thinking are noted.

The respiratory center is inhibited by morphine. Even after therapeutic doses an elevation in the threshold level for the physiological stimulants (e.g., carbon dioxide tension in blood) can be established. The inhibition of the respiratory center is dose-dependent. High doses cause complete paralysis. Death in cases of morphine poisoning is usually due to central respiratory paralysis. The respiratory center of newborns and infants is especially sensitive to opiates. Since these compounds are

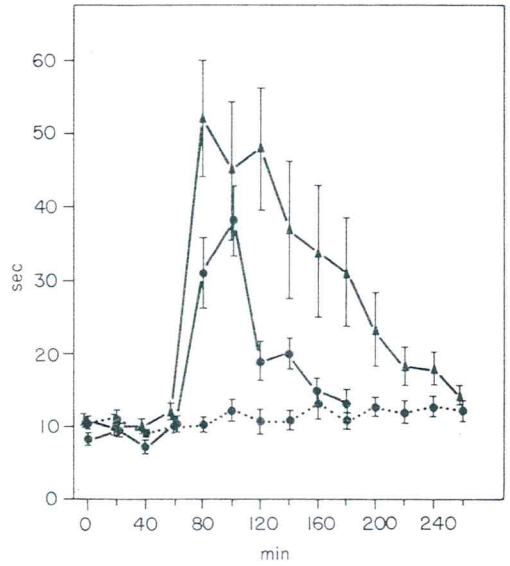


Fig. 46. The analgesic effect of morphine in mice. The pain threshold was determined in the following way. The mice were placed upon a hot plate (57°C) and the time measured in seconds until they lift their front paws to lick them. As the control values show, this time interval is about 10 sec and remains constant despite repeated measurements over 4 hr. Under the influence of opiates this threshold is elevated, i.e., more time is required for the animal to react. If the mouse has not reacted after 60 sec, the experiment is stopped and 60 sec taken as the reaction time. Each group consisted of 6 animals; the mean and standard error of the mean are given ($\bar{x} \pm s_{\bar{x}}$). ●···●, untreated controls; ●—●, morphine 0.006 mg per gram body weight subcutaneously; ▲—▲, morphine 0.02 mg per gram body weight subcutaneously. The analgesic effect of morphine is dose dependent with regard to its intensity and duration.

capable of penetrating the placental barrier, the use of opiates during birth is not allowable. Apart from the respiratory center, the cough center is also inhibited.

Besides the previously described effects, morphine has stimulatory components in its action on the central nervous system. It stimulates the chemoreceptors in the area postrema, which leads to excitation of the vomiting center in some cases. Even therapeutic doses frequently cause nausea and vomiting. Vagal and oculomotor centers are stimulated, leading to increased intestinal tonus, bradycardia, and miosis.

The effect of morphine on the central nervous system can be demonstrated in animal experiments. Morphine and all the other opiates have an analgesic effect on all warm-blooded animals. Figures 46 and 47 show experiments in which changes in the threshold for thermally induced pain under the influence of opiates has been measured. The reaction to opiates appears to have a marked species dependence. The higher the organizational level of an animal, the smaller the dose required for analgesia. In addition, there are species-specific responses. For example, in the mouse after opiates a sign of central excitation is seen in that the tail is elevated over the back and bent into an S-shape (Straub phenomenon) (Fig. 48). In the cat a change in conscious perception appears to occur. An observer has the impression that optical and auditory hallucinations are perceived by the experimental animal following administration of morphine. Environmental stimuli can only transiently interrupt this condition. In dogs, morphine is a very effective emetic.

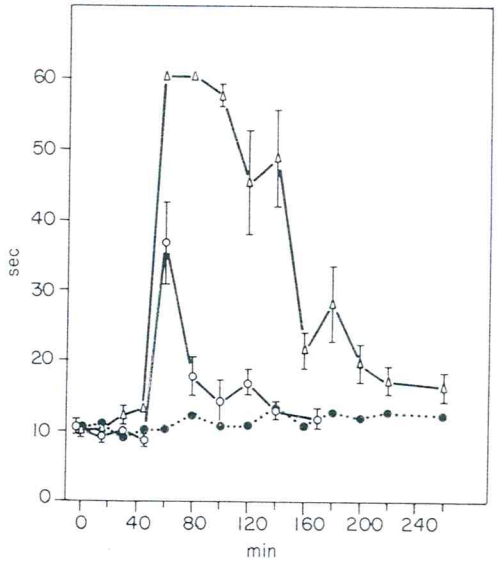


Fig. 47. The analgesic effect of synthetic opiates. Experimental design as in Fig. 46. ●···●, untreated controls; ○—○, methadone 0.005 mg/g of body weight subcutaneously; △—△, meperidine 0.015 mg/g of body weight subcutaneously. The analgesic effect of methadone and meperidine in these doses roughly corresponds to the effects of morphine in the mouse as given in Fig. 46.

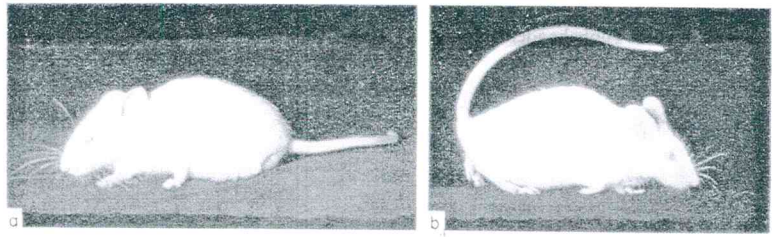


Fig. 48. Typical behavior of a mouse after an injection of an opiate. The lefthand picture shows an untreated mouse, the right an animal which has received 20 min before, 0.02 mg of morphine per gram body weight subcutaneously. Note the position of the tail (Straub effect) and the placing of the hind limbs.

Aside from its central effects, there are peripheral effects of morphine that consist mainly in an elevation of smooth muscle tone (e.g., in the intestinal tract there is a spastic constipation). This increased tonus mainly affects the sphincters, for example, that in the bladder. Micturition becomes impossible, but the overfilled condition of the bladder is not noticed by the patient due to the concomitant analgesia. The same holds true for the pylorus, whereby food is retained for a longer time in the stomach. The "therapeutic" effect of morphine in painful spastic and inflammatory conditions of the urinary and biliary ducts is due to analgesia, not to any local effect; spasms may even be precipitated. Since the stimulatory effect of morphine on smooth muscle is always an undesired side effect, it is advisable to administer atropine simultaneously since this drug partly abolishes the spasmogenic effect. Morphine and other opiates do not significantly influence the tonus and movement of the uterus during birth. The cardiovascular system is influenced by morphine to a negligible extent. Only in morphine poisoning does it become secondarily involved.

After oral administration the morphine effect is weaker than after the same dose administered parenterally. The maximal effect is reached after 30–60 min, while parenteral doses act much faster. Between 40 and 50% of the absorbed morphine is excreted via the kidney, nearly all of it in a conjugated form. Only small amounts are found in the feces. The highest rate of excretion is observed during the first 6 hr after administration, but some morphine excretion can still be demonstrated after 24 hr.

Severe pain that cannot be influenced by other measures or other pharmacological agents is the indication for morphine. Because of the problem of tolerance and the danger of addiction, morphine should never be prescribed lightly. In patients for whom recovery is probable, morphine must be given only for short periods (not more than 2 weeks), in doses that are just sufficient. In terminal conditions it can be given without restrictions. Because of the depressant effect on respiration, morphine is contraindicated if the central regulation of respiration is already compromised (by other drugs, cerebral pressure, etc.) or if the pulmonary surface available for oxygen exchange is diminished, as in pulmonary edema, emphysema, etc.

Long-lasting administration of morphine leads to tolerance. Morphine tolerance is not specific, but holds for all semisynthetic or synthetic opiates. An increase in

the dose becomes necessary after about 3 weeks of daily morphine administration. Tolerance may become very extreme (100 times the initial single dose of 10 mg may be needed). The mechanism responsible for morphine tolerance is unknown, although the phenomenon can be elicited in animal experiments. Since faster excretion of morphine or a more rapid detoxification rate have been ruled out as causes, a mechanism operating at the cellular level seems to be a more likely explanation.

The main symptoms of acute morphine poisoning are coma, respiratory depression, and miosis. The principal aim of therapy, as in acute barbiturate poisoning (cf. p. 164), must be to relieve the oxygen deficiency resulting from the insufficient respiratory activity.

Along with many nonspecific central analeptics, nalorphine is a specific antidote that is active against all opiates (Fig. 49). Nalorphine is *N*-allyl normorphine (the tertiary nitrogen has its methyl group replaced by the allyl group: $-CH_2-CH=CH_2$). Doses between 5 and 30 mg (depending on the seriousness of the case) abolish the

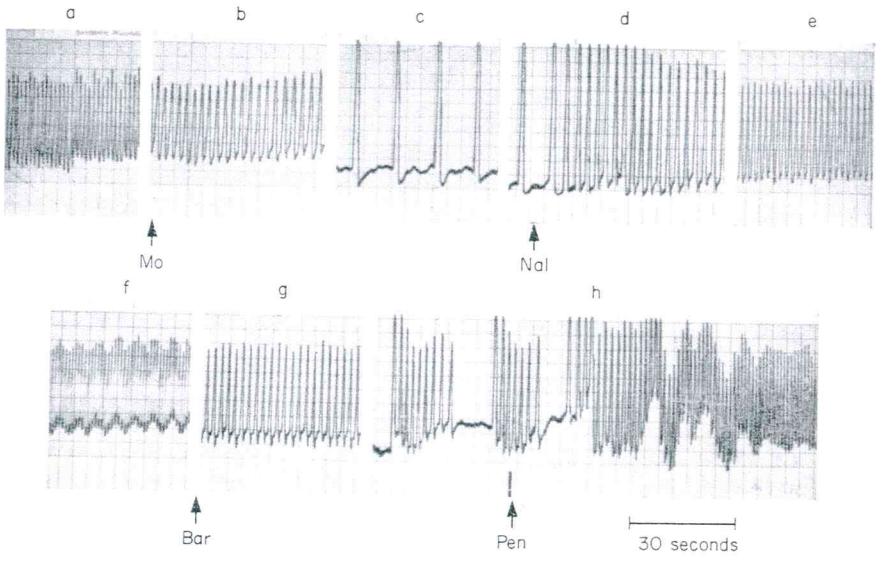


Fig. 49. Influence of drugs on respiration. The excursions of the thorax of a rabbit are recorded. Between (a) and (b) 10 mg of morphine were injected intravenously into the 2-kg rabbit (Mo). (b) Immediately following administration. (c) 5 min later. (d) 7 min later. The result is marked inhibition of the respiratory center. In (d) 1 mg of nalorphine (Nal) was administered intravenously; respiration was immediately improved and reached normal initial values within a few minutes at (e). The lower series shows a corresponding experiment in which between (f) and (g) a barbiturate (pentobarbital 90 mg intravenously) produced respiratory depression. (g) Immediately after the injection. (h) 5 min later (Cheyne-Stokes respiration). At Pen, 100 mg of pentylenetetrazole was injected intravenously; respiration was restored to normal values after a short period of time. The therapy of barbiturate intoxication *in man* with analeptics is not optimal treatment.

respiratory depression caused by morphine. This effect lasts for about 2–3 hr. Nalorphine is not quite as active against the concomitant loss of consciousness. Nalorphine itself has only weak analgesic properties, but elicits central symptoms (giddiness, ataxia, hallucinations, and dysphoria) in persons not under the influence of morphine. The allyl derivative of levorphanol, levallorphan, which is analogous to nalorphine, possesses the same antagonistic activity.

Chronic administration of morphine can produce morphine addiction. It can never be stated with any certainty whether a given person will become an addict or not; this means every patient is potentially in danger. Morphine addiction is characterized by developing euphoria after administration of the drug, a hunger for morphine, and withdrawal symptoms when administration is interrupted. Chronic morphine poisoning leads to anemia, early aging, and loss of weight as a result of reduced appetite. The psychic symptoms depend very much on the complexity of the personality involved and on his social environment. The ethical behavior of the addict drops rather quickly, but intelligence may not be affected for a long while. The hunger for morphine and the fear of withdrawal symptoms induce the addict to use illegal means in order to obtain a supply of the drug. The picture of the addict is thus determined not only by the pharmacological effects of morphine but also by the social environment and ease or difficulty with which he can obtain the opiate. Since members of the medical profession have especially easy access to morphine, the highest percentage of addicts is found among them. On the other hand, one finds a smaller percentage of gross criminal acts among members of the medical profession than among addicts from a low social level.

Withdrawal symptoms occur in addicts if the taking of the opiate is interrupted. They start about 6–12 hr after the last dose of the drug, with a strong desire for morphine. Following this, psychic and autonomic symptoms develop, such as unrest, depression, excitability, weakness, diarrhea, circulatory failure (occasionally life-threatening), stenocardia, vomiting, sweating, lacrimation, etc. This syndrome may last for 1–2 weeks. It can be relieved immediately by the administration of an opiate. Withdrawal symptoms also occur in addicts upon the administration of nalorphine. By the time the withdrawal symptoms have faded, one usually finds that the tolerance also has been overcome, and usual doses are again able to cause euphoria. Tolerance and withdrawal symptoms can also be evoked in higher animals. A cure from morphine addiction only can be effected in institutions capable of giving psychotherapeutic treatment at the same time; even under these circumstances relapses are frequent.

Morphine Derivatives

All morphine derivatives given in Table V have qualitatively the same action as morphine. They cause analgesia and euphoria. They are addictive and are able to completely replace morphine in addicts. In general, they do not offer any advantages over morphine. Individually some opiates may cause fewer side effects than morphine, but the opposite is also possible.

Diacetylmorphine (heroin) must be singled out especially. The danger of addiction is much greater than with other morphine derivatives and it can be sniffed.

TABLE V

Compilation of Some Morphine Derivatives

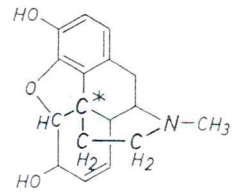
Generic name	Chemical constitution	Single therapeutic dose
Hydrocodone	Dihydrocodeinone	5–10 mg p.o.
Thebacon	Dihydrocodeinone enol acetate	2.5–5 mg p.o.
Oxycodone	Dihydrohydroxycodeinone	10–20 mg s.c.
Hydromorphone	Dihydromorphinone	2 mg s.c.
Levorphanol	*l*-3-Hydroxy-*N*-methyl-morphinan	1.5 mg s.c. or p.o.
(completely synthetic)		
Heroin	Diacetylmorphine	1 mg
		Not to be used.
		(Illegal in the U.S.)

Heroin must not be used under any circumstances as a pharmacological agent. The manufacture, importation, or possession of heroin or its salts is forbidden in the United States by federal law. Withdrawal treatment with heroin addicts remains almost always unsuccessful. The continuous treatment with high doses of methadone given by mouth offers the best chance for resocialization. The patients remain addicted to methadone.

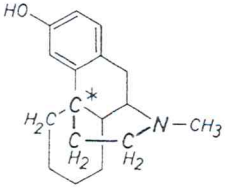
Synthetic Narcotic Analgesics

The synthetic compounds meperidine, methadone, ketobemidone, dextromoramide, and levorphanol act like morphine, i.e., they can be used as analgesics under the same conditions and with the same reservations as indicated for morphine above. It should be pointed out again that these synthetic opiates have the same side effects as morphine: paralysis of the respiratory center, euphoria, and addiction. In principal there is no advantage to the use of these compounds compared to morphine. Nevertheless, they can be given orally without much loss of activity. Although all drugs currently available that possess the analgesic potency of morphine are addictive and depressants of the respiratory center, these properties do not seem to be necessarily coupled. In acute cases of poisoning, nalorphine is active as an antidote. To satisfy the craving of an addict, the semisynthetic and fully synthetic compounds are freely interchangeable. This indicates that addiction caused by any of the new synthetic opiates should be treated in the same manner as morphine addiction.

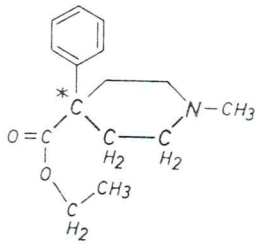
Meperidine has a weaker analgesic effect than morphine—the single dose for an adult without tolerance being about 50 mg, which is equivalent to 10 mg of morphine. The increase in smooth muscle tonus following meperidine appears to be less than after morphine. Nevertheless, the precipitation of biliary colic as the result of increased tonus after meperidine has been reported. Methadone is somewhat more potent than morphine. It is orally active; nausea and vomiting occur frequently and it is, therefore, commonly combined with an atropinelike compound. Ketobemidone has about two times the analgesic potency of morphine. Since its euphorigenic properties appear to be especially marked, this compound should not



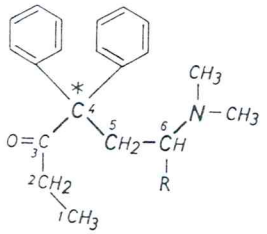
Morphine
Ther. dose 10 mg



Levorphanol
Ther. dose 2 mg

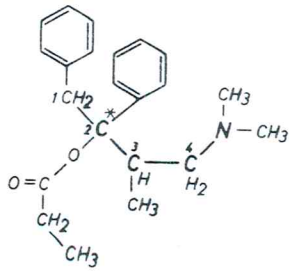


Meperidine
Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate
Ther. dose 50 mg

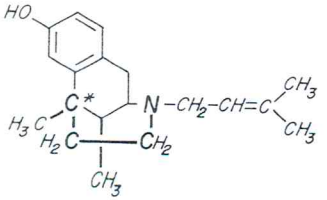


R = CH_3
Methadone
6-Dimethylamino-4,4-diphenyl-3-heptanone
Ther. dose of l-methadone 5 mg.

R = H
Normethadone
6-Dimethylamino-4,4-diphenyl-3-hexanone
Ther. dose 7 mg



Dextropropoxyphene
(α-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol propionate
Ther. dose 60 mg



Pentazocine
1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol

be used. Likewise, dextromoramide is also highly addictive, according to present knowledge, and its use offers only disadvantages. Levorphanol (the *l*-isomer) also possesses a strong analgesic effect, the adult single dose being about 1–3 mg. Levorphanol is tolerated by some patients who do not tolerate morphine. Dextrorphan (the *d*-isomer of levorphanol) has no analgesic or addictive properties, but it inhibits the cough reflex. The methyl derivative, dextromethrophan, has also found application as an antitussive.

Propoxyphene is closely related chemically to methadone (see structural formulas, p. 153); its analgesic action is weak and similar to that of codeine or acetylsalicylic acid. Cases of addiction are extremely rare.

Pentazocine still contains in its molecule important parts of the morphine skeleton. The side chain at the nitrogen, however, consists of a dimethylallyl residue. The analgesic activity of the drug is comparable to that of morphine, but it is probably the sidechain that is responsible for a dysphoric component of its action similar to that observed in allyl-substituted opiates (e.g., nalorphine) rather than the euphoric effect of morphine. Because of these properties this drug, at least when given by mouth, does not give rise to the development of addiction. Therefore, this compound seems to represent genuine progress in comparison with the semisynthetic and synthetic opiates available until now. The side effects are similar to those of morphine, e.g., nausea and vomiting. After excessive doses the respiratory center is paralyzed. Nalorphine is not an antidote. In case of severe pain 50–100 mg should be given orally.

Opium

Apart from 10% morphine, opium contains the secondary alkaloids described on page 146. If an analgesic effect is required, the pure alkaloid morphine is preferable to opium. If, however, additional spasmolytic activity is desired, which is the case in all conditions of severe pain accompanied by spasms of smooth muscle, injectable opium preparations may be utilized. In small doses opium is still used for relaxation of the intestine, since this preparation does not cause spastic constipation as does morphine, but rather an atonic constipation because of its papaverine content. For this purpose single doses of 50–100 mg opium or 0.5–1 gm tincture of opium are required for adults.

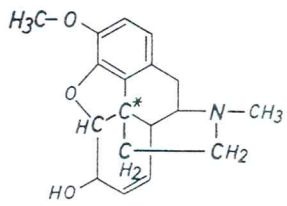
Antitussives

Antitussives are pharmacological agents capable of inhibiting the cough reflex by an action in the central nervous system on the cough center. Coughing may be elicited peripherally upon irritation of mucous membranes of the bronchi or by bronchoconstriction. Centrally induced coughing also occurs. Antitussives are useful for the suppression of a dry cough but are not indicated when large amounts of bronchial secretion are present.

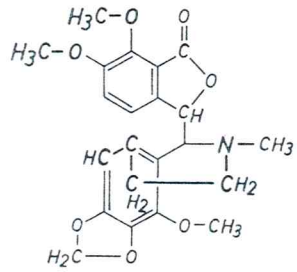
The effectiveness of antitussive agents in man may be tested by means of the suppression of coughing, induced upon respiration of aerosols of 5–25% solutions of citric acid.

As was pointed out in the discussion on the active centers in the morphine molecule, alkylation of the phenolic hydroxyl group weakens the analgesic effect of the compound. The ability to inhibit the cough center remains largely unaffected, and such compounds possess excellent antitussive properties.

For codeine (methylmorphine) the inhibitory effect on the cough center predominates completely in therapeutic doses of 30–50 mg for an adult. The analgesic effect is very weak, while euphoria and codeine addiction are practically never observed with oral administration. The side effects, which may interfere with its use as an antitussive, are occasional constipation, nausea, and respiratory depression. The injection of large amounts of codeine can satisfy the craving of opiate addicts because small amounts of morphine are formed in the body as the result of demethylation. The analgesic effect of codeine is utilized in a number of mixed preparations by combination with other analgesics.



Codeine
Methylmorphine



Narcotine
Noscapine

Ethylmorphine in corresponding doses has effects similar to those of codeine, with the same side effects. Dextromethorphan has no analgesic component in its action and does not cause addiction while the antitussive effect is good in doses of 15–30 mg. Side effects are rare. Narcotine stops cough (50–100 mg) without interfering with intestinal function or the respiratory center.

Normethadone (see the similarity with methadone in the structural formula) has typical opiate effects. Besides euphoria, addiction, analgesia, and respiratory depression, there is also depression of the cough center.

Expectorants

Compounds that provoke increased expectoration by liquefying bronchial secretions (secretolytics) or by increased transport of bronchial mucus (secretomotor agents) are included in the class of expectorants. Their use is usually purely empirical, and the mechanism of action is not always verified. They are effective only after administration of sufficient fluids.

The most probable mechanism of action for a number of compounds is an irritation of the gastric mucosal lining, which leads by reflex action to stimulation of the vagus, thus causing increased bronchial secretion. This is presumably the mechanism by which several salts (e.g., ammonium chloride) and the saponin-containing drugs (*Radix senegae, Radix saponariae, Radix primulae*) exert their effect. Preparations containing sugars (maltose, licorice) may act via a reflex increase in secretion from the mucous lining of the mouth. Emetics, such as ipecac, have an expectorant action by irritating the stomach lining. However, some of the activity can be attributed to the nausea developed which in itself results in increased bronchial secretion. Essential oils have weak spasmolytic effects (oils of thyme, anise, and eucalyptus). A combination of expectorants with antitussives is not recommended, since the elimination of bronchial mucus requires an effective cough reflex.

Mucolytics

Aerosols of *N*-acetylcysteine solutions (10–20%) liquefy viscous bronchial exudate, such as is found in bronchiectasis. The mechanism consists of rupture of disulfide bonds in the large exudate molecules, thereby lowering the viscosity of the mucus.

CHAPTER 4

THE BRAIN

Hypnotics

Hypnotics or sleep-inducing drugs do not constitute a sharply defined pharmacological group. Rather, quantitative considerations are involved. In the proper dose the compounds are hypnotics; smaller doses have only a sedative effect, and larger ones are anesthetic. An example of this is the barbiturates. Phenobarbital in small doses (15 mg) is a sedative and in a higher dose (200 mg) an effective hypnotic. Oral administration of 250 mg of hexobarbital gives a hypnotic effect; the intravenous administration of 500 mg of sodium hexobarbital causes general anesthesia. Thus it can be established that every hypnotic can be used as a sedative in the correct dose. However, the converse of this rule is not correct in that compounds have been found that are only weakly active as hypnotics and not active at all as anesthetic agents. Such compounds are not classified as sedatives but are called tranquilizers and belong to the group of psychopharmacological agents. The sedatives are thus treated under the group heading "psychopharmacological agents" (cf. p. 200).

Indications

Little is known about sleep, its causes, and its control. Nevertheless, increasing knowledge concerning orthodox and paradoxical (REM = rapid eye movements) phases of sleep has resulted in some clues concerning disturbances in sleep. The REM phases probably represent periods of increased cerebral activity during sleep, in which the dreams take place. For the regenerative function of sleep these

phases are as important as the periods of "orthodox" sleep. Continuous suppression of REM sleep provokes psychic disturbances (even the occurrence of psychotic symptoms). Hypnotics in the usual doses influence the REM phases in a different manner: barbiturates (and compounds of similar structure) inhibit the REM periods, chloral hydrate and benzodiazepine derivatives do not influence these phases of sleep. After the abrupt discontinuation of barbiturates, the occurrence of REM phases is intensified for a long time (more frequently with dreams accompanied by fear). If prior to drug withdrawal, a genuine physical dependence on barbiturates existed, delirium may even be elicited.

A person is not fully capable or productive if his sleep is chronically disturbed. Medical treatment is necessary and may include the prescription of sleep-inducing drugs. Before this step is taken, however, the physician should attempt to elucidate the cause of the disturbed sleep. Many reasons can lead to this condition, some of which are listed here—chronic pain, surroundings inadequate to induce restful sleep (too much noise, light, or heat), an unhealthy mode of life (too many stimulants during the day, little physical activity, large and heavy meals at night, etc.) and internal (cardiac insufficiency, etc.), psychopathological, and neurological processes. These conditions require primarily a treatment designed to eliminate the causes. Distinct from these, one should recognize conditions resulting from mental or psychological stress that cannot be eliminated easily. Included here might be occupational stress involved in modern life and mental anguish. Basically, one should prescribe hypnotics only if a causal therapy is either not possible or not successful. If chronic administration of hypnotics cannot be avoided, the drug should at least be changed occasionally. The new drug should belong to a completely different chemical group. Since most hypnotics are chemically related to the barbiturates, the use of a tranquilizer, e.g. nitrazepam, from the group of the benzodiazepine derivatives is to be recommended (p. 201). This drug would seem to be especially suitable in cases of despairing anxiety resulting from the chronic loss of sleep. On the other hand, following prolonged use of hypnotics many weeks may be required before the sleep rhythm and other neurophysiological functions are again normal.

Depending on whether the problem lies in an inability to fall asleep or to sleep through the night without interruption, different pharmacological agents are indicated. To enable a person to fall asleep quickly, fast-acting agents with a short duration of action are indicated. The treatment of insomnia that interrupts sleep requires longer-acting compounds; the onset of action may then be slow.

Alcohols

Ethanol has hypnotic or anesthetic properties, depending on the dose taken. In some persons ethanol causes symptoms comparable to some symptoms of the excitation phase of ether anesthesia. On the basis of its properties ethanol can be used only rarely as a hypnotic. It should be mentioned that various types of alcoholic beverages can act quite differently in one and the same individual. This is not the result of variation in the alcohol content, but of the presence of additional

compounds contained in the particular beverage. Thus, beer in general tends to act as a sedative while some wines tend to be excitatory. Due to its widespread consumption in beverages, alcohol is of great toxicological interest and is discussed more thoroughly in the section on toxicology. Paraldehyde, a polymer composed of three molecules of acetaldehyde, is more potent than ethanol. In a dose of 3–10 ml (pure compound) given orally, rectally, or intramuscularly in appropriate dilution, this drug is very useful for producing sedation in agitated patients.

More active hypnotics are produced by the introduction of halogen atoms into alcohols (also see anesthetics, chloroform, p. 173). Chloral hydrate is a chlorine-containing aldehyde hydrate which is a good hypnotic. It is metabolized to trichloroethanol in the organism. The hypnotic dose in adults is about 0.5–1.5 gm (compare to the equipotent dose of ethanol, about 20 gm). Chloral hydrate is absorbed quickly from the intestinal tract; the duration of action is about 5 hr, and in the morning there is no hangover. A disadvantage of chloral hydrate is its irritant effect on mucous membranes. Therefore, it should be prescribed with an emulsifying agent (traganth, oatmeal, or milk) or given in capsules. An alternative is rectal administration.

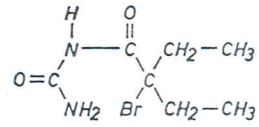
With daily administration chloral hydrate rapidly loses its effectiveness. Since halogenated hydrocarbons can cause liver damage, chloral hydrate is contraindicated in persons with liver disease; it also should not be given in cardiac insufficiency. Because of its local irritant action, oral use in the presence of gastric disorders should be avoided. Acute poisoning by chloral hydrate (after doses of 3–5 gm and higher) shows similarities to that of other hypnotics; however, its onset is very rapid due to the ease of its absorption. Chloral hydrate intoxication should be treated in the same way as that of other hypnotics (cf. p. 164).

Urea Derivatives

Monoureides

In contrast to the cyclized urea derivatives (e.g., barbituric acid), carbromal and bromisovalum are collectively called monoureides. Carbromal and bromisovalum are mild hypnotics, quickly absorbed from the gastrointestinal tract, with an effect lasting for 3–4 hr. A single dose is about 0.5–1.5 gm, and side effects seldom occur at such a dosage level. However, cases of purpura have been observed following carbromal. Both compounds are suitable for treating slight disturbances of the sleep pattern. Similarly to barbiturates, these drugs can also produce habituation in relatively rare cases.

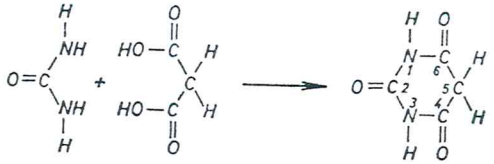
Urea derivatives



Carbromal
α-Bromodiethylacetylurea

Barbituric Acid Derivatives

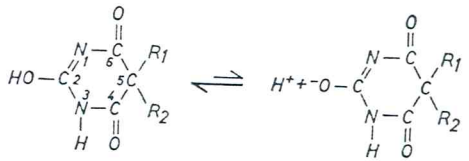
Barbituric acid can be viewed as the condensation product of urea and malonic acid, and this type of condensation is a mode of synthesis.



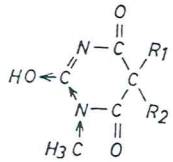
Urea Malonic acid Barbituric acid

2,4,6-Trioxohexahydropyrimidine

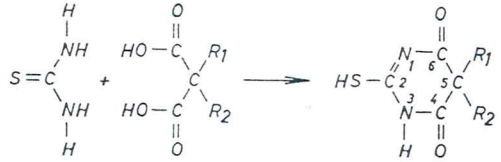
Barbituric acid is highly dissociated and therefore a rather strong acid—stronger than acetic acid. The hypnotic and anesthetic effects of barbituric acid are related to the free, undissociated form of the acid; the ionized form is pharmacologically inactive. The high degree of dissociation of barbituric acid explains why this compound itself has no activity. If the hydrogen atoms on carbon-5 are substituted, the resonance in the pyrimidine ring is hindered, the oxygen on carbon-2 remains more strongly electronegative, and the dissociation of the hydrogen is largely suppressed.



A further reduction of such dissociation can be obtained by a further chemical modification. Here, for example, the electron-donating (positive-inductive) effect of a methyl group substituted on nitrogen-3 may be utilized. This group of *N*-substituted barbiturates includes the rapidly acting and powerful hypnotics, hexobarbital and mephobarbital.



As described above, a barbiturate is pharmacologically active only as the free acid. It is probable that the relative fat solubility of the free acid and the barbiturate ion is the basis for this phenomenon; only the free acid has sufficient lipid solubility to reach the site of action. Another possibility for increasing fat solubility consists in starting from thiourea instead of urea.



Thiourea Substituted malonic acid Thiobarbiturate (enol form)

The onset of action for thiobarbiturates is very rapid; their duration of action, very short. Both effects are due to the high degree of lipid solubility.

The effect of barbiturates is influenced by the nature of the substituents at carbon-5. The extension of the chain length in the substituent of up to five or six carbons increases the effectiveness and decreases the duration of action of the molecule so formed. Unsaturated short chains are more active than comparable saturated chains. Branched chains and cyclic substituents decrease the duration of action. Very long chains in aliphatic substituents on carbon-5 or on both nitrogen-1 and -3 lead to compounds that are no longer hypnotics but act as convulsants (e.g., (+)-5-[1,3-dimethylbutyl]-5-ethylbarbituric acid although the (−) form has hypnotic properties).

The Action of Barbiturates

All barbiturates introduced into medical practice have the same type of effect. Differences between them are only quantitative. Their main effect is an inhibition of the central nervous system, which is expressed as a sedative, hypnotic, or anesthetic action. Even doses that exert a good hypnotic action barely affect the functions of the other organs. Sleep induced by barbiturates corresponds objectively and subjectively to physiological sleep. Despite numerous investigations with biochemical and physical methods, it has so far not been possible to elucidate the actual mechanism of action of barbiturates and related hypnotics. Some findings suggest that ion permeabilities of cerebral cells during the preexcitation phase may be specifically inhibited.

An additional central activity is the anticonvulsive component of barbiturate action. This is dose dependent and may be utilized clinically for the treatment of motor hyperexcitability (epileptic seizure, poisoning with local anesthetics, or pentylenetetrazole). A more specific antiepileptic effect is a property of only a few barbiturates (mephobarbital and phenobarbital). The barbiturates have no analgesic component in their overall effect; they do not suppress pain. Hyperalgesia may even appear under certain conditions. Interneurons in the spinal cord are inhibited, but only very high doses suppress spinal reflexes. Barbiturates inhibit

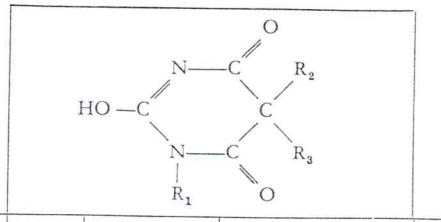
the respiratory center, an effect of little importance in hypnotic doses except in cases of chronic emphysema.

Choice of Barbiturates

Depending on the type of sleep disturbance, the hypnotic must be either a sleep-inducing or a sleep-maintaining drug. With those maintaining sleep, it is again of some importance how long the action should last. It must be assumed that a man who is working should be able to take up his activity after 7 hr of relaxing sleep. Table VI contains the most important barbiturates on the basis of

TABLE VI

Compilation of Barbiturates According to Duration of Activity



Use	Name	R_1	R_2	R_3	Average oral hypnotic dose (grams)	Duration of action
Induction of sleep	Hexobarbital	$-CH_3$	$-CH_3$		0.25–0.5	Short
	Pento-barbital	—H	$-CH_2-CH_3$	$-CH(CH_3)-CH_2-CH_2-CH_3$	0.1	Relatively short
Maintenance of sleep	Hepta-barbital	—H	$-CH_2-CH_3$	 (7-membered ring)	0.1–0.2	Intermediate
	Cyclo-barbital	—H	$-CH_2-CH_3$		0.1–0.2	Intermediate
	Apro-barbital	—H	$-CH(CH_3)_2$	$-CH_2-CH=CH_2$	0.1–0.2	Intermediate
	Butal-lylonal	—H	$-CH(CH_3)-CH_2-CH_3$	$-CH_2-C(Br)=CH_2$	0.2–0.3	Intermediate
	Pheno-barbital	—H	$-CH_2-CH_3$		0.1–0.2	Long
	Mepho-barbital	$-CH_3$	$-CH_2-CH_3$		0.1–0.2	Long
	Barbital	—H	$-CH_2-CH_3$	$-CH_2-CH_3$	0.25–0.5	Too long

their indications. Among the large number of derivatives (more than 1000) that have been tested, only a few have been found necessary in practical medicine.

Metabolism of Barbiturates in the Organism

Barbiturates as acids or salts are well absorbed from the gastrointestinal tract. They are bound to plasma proteins in differing degrees. Only the *N*-substituted barbiturates and the thiobarbiturates are extremely lipid soluble (concerning the redistribution phenomena, see p. 177). Other barbiturates are eliminated from the body by degradation and renal excretion. The quantity, which is eliminated unchanged, differs very much for each barbiturate. Barbital, for instance, is excreted up to 90% in the unchanged form. Hexobarbital is almost completely metabolized. The chemical degradation of barbiturates occurs mainly in the liver. The following processes have been found—(1) oxidation and dealkylation of the side chains in position 5, (2) loss of the alkyl group from the nitrogen, (3) opening of the ring although quantitatively of less importance, and (4) a desulfuration of thiobarbiturates. The rate of detoxification differs considerably from one barbiturate to another. The one extreme is represented by barbital or phenobarbital, the concentration of which in the body drops by only 20% daily; the other by hexobarbital, the degradation and excretion of which are accomplished within a few hours. Following repeated doses most barbiturates are more rapidly metabolized than after the first dose. The reason for this is an increase in the activity of the corresponding enzymes (see enzyme induction, p. 325). This mechanism leads to increased tolerance to barbiturates. Enzyme induction is one of the few basic processes determining tolerance which has been elucidated. Since the enzymes are unspecific, other compounds as well as barbiturates are more rapidly inactivated.

Side Effects of Barbiturates

Side effects are rare after hypnotic doses. Occasionally allergic hypersensitivity reactions such as skin edema and drug exanthema are observed. Cases of exfoliative dermatitis have been found following phenobarbital. In very sensitive individuals even small doses may cause the symptoms of a long-lasting hangover.

In some people barbiturates do not act as hypnotics or sedatives, but as stimulants. Such stimulation may contain a euphoric component, i.e., the necessary characteristic for generating an addiction of a type occurring more and more frequently. Barbiturate addicts take the drugs for the euphoria and excitation that are induced and attempt to suppress the symptoms of central depression (such as ataxia and speech disturbances) by taking psychoanaleptics.

The fact that compounds which inhibit the central nervous system can also act as stimulants is not as surprising as it may initially appear. Thus the usual barbiturates have an excitatory effect in some animals; anesthetic agents in small doses also result in stimulation (excitatory stage); certain barbituric acid derivatives excite (cf. p. 161); and a chemically related β-substituted glutarimide is used

as an analeptic. The excitatory and the inhibitory effects are therefore closely associated.

Barbiturate Poisoning

Since barbiturates are readily available, there is a relatively high frequency of accidental, and particularly suicidal, cases of poisoning. Of course, the severity of the poisoning depends on the dose taken. Typical symptoms are (1) loss of consciousness, which may be preceded by a delirious excitatory stage, (2) central respiratory depression with symptoms of hypoxia, (3) circulatory failure in the last stages of poisoning, and (4) secondary influence on other bodily functions such as kidney function, which is usually depressed, or the body temperature, which decreases, although it may be increased if bronchial pneumonia is present. Death occurs, depending on the individual case (barbiturate used, dose, and subject's state of health), after 12 hr to 4 days and is caused by tissue anoxia, circulatory insufficiency, disturbances in water and electrolyte metabolism, or bronchial pneumonia. The prognosis depends very much on the time elapsed between the ingestion of the barbiturate and the beginning of treatment.

The immediate goal of any treatment is an attempt to alleviate the danger caused by respiratory depression. The most important steps are artificial respiration (with oxygen) and maintenance of the patency of the respiratory passages. The circulation should be constantly observed and if necessary treated symptomatically. Infusions of plasma are indicated if shock is imminent or has already set in. Gastric lavage to remove the ingested barbiturate is sensible only if performed a short time after the drug has been taken. Aspiration of the stomach contents into the trachea must absolutely be avoided (tracheal intubation). To decrease the level of barbiturate in the body in particularly severe cases, forced osmotic diuresis with mannitol, exchange transfusions, and hemodialysis have been used successfully. Additionally, water and electrolyte balance must be carefully maintained, and antibiotics should be given prophylactically to avoid infection.

Treatment with analeptics (pentylenetetrazole and bemegride), which formerly was the only measure taken and is still utilized today, has become outmoded in view of the above procedures (for further discussion on the advantages and disadvantages of analeptics, cf. p. 205). If they are to be used, the dose should depend on whether the patient's respiratory function has been reestablished (Fig. 49) and not on whether full consciousness has returned. The prognosis for barbiturate poisoning has become much more favorable with the adoption of the above supportive measures in comparison to that achieved with analeptics alone. (In the Scandinavian countries mortality has been decreased to a tenth of the previous level.)

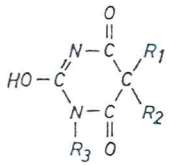
Chronic Abuse of Hypnotics

Two situations must be distinguished in abuse of hypnotics: (1) patients that react to hypnotics in a normal way but have acquired the habit of ingesting large

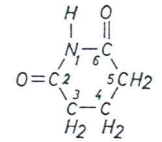
amounts of drugs every night (habituation), and (2) persons that behave in an abnormal fashion following ingestion of hypnotics (euphoria), and thus can become addicted. The behavior outlined under (1) above is relatively harmless, and it is nearly always possible to free the patient from this bad habit. True addiction to barbiturates or other hypnotics is much more serious. Evidence that it represents a true addiction is seen in the increased tolerance (need to increase the dose), the uncontrolled desire for drugs, and the withdrawal symptoms—fear, weakness, nausea, tremor, epileptiform convulsions. Treatment should be undertaken in a psychiatric department. Addicts may suffer from delirium tremens, with symptoms not distinguishable from those caused by alcohol.

Piperidine Derivatives

The hypnotics, glutethimide, methyprylon, and pyrithyldione have the same qualitative effects as barbiturates. The doses necessary for hypnotic effects are 0.2–0.5 gm. They are thus somewhat weaker acting than the comparable, moderately long-acting barbiturates. They do not appear to offer any advantages over the barbiturates in that a dependence with all of its consequences may equally develop with chronic use.

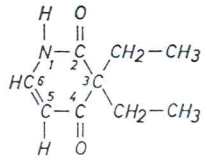


Barbituric acid derivative
(Pyrimidine derivative)
(f. Table VI)

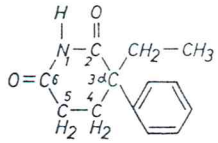


Glutarimide
2,6-Dioxopiperidine

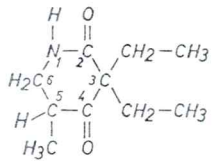
Piperidine derivates



Pyrithyldione
3,3-Diethyl-2,4-(1H,3H)pyridinedione

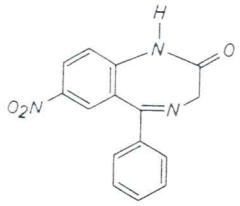


Glutethimide
α-Ethyl-α-phenylglutarimide



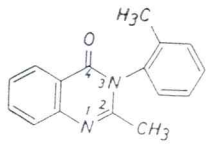
Methyprylon
3,3-Diethyl-5-methyl-2,4-piperidinedione

Benzodiazepine derivative



Nitrazepam
1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepine-2-one

Quinazolinone derivative



Methaqualone
2-Methyl-3-o-tolyl-4-(3H)-quinazolinone

Quinazolone Derivatives

Methaqualone belongs to a completely different chemical group. Its pharmacological effects resemble those of the barbiturates. The effect is moderately long. Occasionally it elicits symptoms of agitation. In toxic doses, in contrast to other hypnotics, the foremost symptoms are excessive motor activity, hyperreflexia, and convulsions.

Benzodiazepine Derivatives

Nitrazepam, closely related to the tranquilizer, diazepam, can be effectively utilized as a hypnotic. The single dose is between 5 and 10 mg.

Antianxiety Drugs

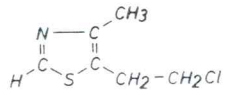
Scopolamine

Apart from its parasympatholytic effect (cf. p. 17), scopolamine has a marked sedative action that can be used to calm excitable mental patients (dose, 1 mg several times daily subcutaneously). Usually stupor and apathy develop and there is retrograde amnesia following the use of the compound (the truth serum

of the popular press). In exceptional cases symptoms of excitation may develop. The site of action is presumably in the brain stem, as is also indicated by its favorable effect in Parkinsonism (cf. 130).

Chlorethiazol

Pharmacological investigation of fragments of the thiamine molecule showed that some thiazole derivatives exhibit a central depressant effect. The compound having the most favorable therapeutic effect is chlorethiazol. The foremost indication is the excitatory stage in delirium tremens and cerebral sclerosis. The drug also can be tried in other types of agitation; for delirium tremens it is superior to other therapy. It can be given in daily doses of 5–8 gm or with great caution intravenously as a prolonged infusion. Higher doses may result in respiratory depression, necessitating artificial resuscitation. During intravenous administration the systolic blood pressure may fall by 10 or 20 mm Hg.



Chlorethiazole
5-(2-Chloroethyl)-4-methylthiazole

Diazepam

This benzodiazepine derivative (cf. p. 201) is apparently a good drug against agitation. It is used in conjunction with the usual therapy in cases of delirium tremens, as well as in tetanus traumaticus, and status epilepticus. The muscle relaxant activity is produced by the inhibition of polysynaptic reflexes (cf. p. 129).

Antiemetics

Antiemetic agents belong to the following classes of drugs: cholinolytics, antihistamines, and neuroleptics. Metoclopramide cannot be classified satisfactorily. Antiemetics have gained increasing importance for the prevention of motion sickness. They may also be indicated in morning sickness during pregnancy. For the treatment and prophylaxis of motion sickness (precipitated by travel on boats, planes, cars, or trains), the following compounds have been found useful: scopolamine, about 0.5–1.0 mg orally 1 hr before the trip, and every 4 hr thereafter, and meclizine and dimenhydrinate, 50 mg orally, 30 min before the journey, and thereafter up to 100 mg every 4 hr. The exact site of action and mechanism of action are unknown. Dimenhydrinate and other agents related to antihistamines should not be given during the first trimester of pregnancy.

If an antiemetic is necessary to suppress vomiting during pregnancy which dangerously threatens electrolyte balance, promethazine, chlorpromazine (about two times, 25 mg), and perphenazine (three to four times, 4 mg) have been found

useful. Chlorpromazine is relatively ineffective in motion sickness. It is highly probable that the site of action of chlorpromazine is the chemoreceptor zone of the area postrema, where the vomiting process is initiated. Piperazine-substituted derivatives of chlorpromazine are even more active than the parent compound, including vomiting induced by other causes. Metoclopramide, 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-*o*-anisamide, possesses an antiemetic effect by influencing the area postrema. Another central action results in gastric emptying. The drug is suitable for symptomatic treatment of nausea, vomiting, and singultus.

Anesthetics

The term anesthetic cannot be exactly defined although the clinical symptoms can be described and characterized. Various compounds that are called anesthetics on the basis of their typical effects lead to reversible changes in the central nervous system, causing loss of consciousness and a state allowing surgical procedures to be performed without pain and defensive reactions. The lack of a more exact definition is simply the result of a deficiency in our understanding of the process on which anesthesia is based. In spite of intensive investigations involving pharmacological, physicochemical, and clinical research, the changes in the central nervous system causing anesthesia remain unknown. The existence of many theories of anesthesia should not blind us to the fact that we lack knowledge. Furthermore, the mass of data assembled on the influence of anesthetics on brain tissue and interpreted from physical, biochemical, and pharmacological viewpoints should not interfere with the recognition that the mechanism of action and the actual site of action are unknown for anesthetic agents.

The many theories proposed over the last six decades are in part not theories of anesthesia but theories concerning the distribution and activity of anesthetics and in part are speculations on how one might imagine the mode of action. From a didactic point of view, it appears unprofitable to deal with these theories in detail here. The interested reader is referred to monographs on anesthesia. In principle all theories of anesthesia must explain how compounds of quite different types, some of which are chemically inert (such as xenon, a noble gas), others of which are rather reactive, are able to bring about a reversible change in the functions of the central nervous system in such a way that loss of consciousness and insensitivity to pain occur. The large number of anesthetics of completely different chemical structure (noble gases, alcohols, ethers, halogenated and unsaturated hydrocarbons, barbiturates, and steroids) render a common mechanism questionable. The activity of noble gases—compounds that do not take part in any chemical reaction—leads to the conclusion that purely physical changes on or in nerve cells are sufficient to attain the alterations in function resulting in anesthesia. Alterations in cell membrane permeability, or the occupation of active surfaces, are in the forefront of these physical theories. The mechanism of action of reactive anesthetics has been sought in an inhibition of enzymic processes. However, conclusive evidence for the existence of such a mechanism specific for anesthetics has not been presented yet. There remains the question of whether or not a universal theory of

anesthesia is at all possible. It may be that completely different cellular mechanisms give the same overall effect. Anesthesia would then be a monotonic response to very different types of interference with the functions of nerve cells.

The effect of anesthetics is not restricted to nerve cells in the central nervous system, but rather, the function of all cells of the body is affected. The decision whether or not a compound can be used as an anesthetic agent is determined by the extent to which the brain cells are more sensitive than other cells. In addition, different regions of the central nervous system must respond in a certain sequence: first the cerebrum and the spinal cord, and much later the autonomic centers in the brain stem.

In practice, a differentiation of different stages of anesthesia has been found very useful.

1. Analgesic stage. Only the higher cortical centers are inhibited; sensitivity to pain is reduced; and consciousness is partly maintained.
2. Excitation state. The inhibition of higher motor centers releases lower ones; with loss of consciousness, motor hyperactivity dominates.
3. Stage of surgical anesthesia. The midbrain and the spinal cord as well as the cortex are inhibited; skeletal muscle tonus is decreased; there is complete loss of consciousness; reflexes are inhibited to some extent; circulatory and respiratory centers are still functioning sufficiently. During this stage, which can be divided into four planes, the patient is in a state that allows surgical intervention.
4. Paralytic stage. The autonomic centers in the brain are inhibited; respiration and circulation fail, and the life of the patient is in danger.

Satisfactory anesthesia should fulfill three requirements.

1. Loss of consciousness
2. Complete analgesia and loss of pain reflexes
3. Muscle relaxation

"Simple" (and obsolete) anesthesia was maintained exclusively by a single anesthetic agent and considerable doses of anesthetic had to be given to achieve the third requirement. However, this results in an overdosing of the agent in terms of the first two requirements. For this reason, the more modern "combination" anesthesia represents an important advance. The three requirements are achieved separately. The following example illustrates this point. Analgesia is elicited with a narcotic analgesic, unconsciousness with nitric oxide, and muscle relaxation with *d*-tubocurarine. Of course many other combinations are possible. Since "combination" anesthesia is significantly safer for the patient than that obtained with a single agent, it is the preferred form of anesthesia.

Inhalation Anesthetics

The inhalation anesthetics are either liquids with a low boiling point (ether, chloroform, halothane, and ethyl chloride) or gases such as nitrous oxide and ethylene. Major differences in activity between these two groups appear to be

nonexistent. For the maintenance of the stage of surgical anesthesia, the thermodynamic activity of individual anesthetics within the brain is practically identical for all compounds. Since the agents have widely differing solubilities in water, blood, or lipids, the concentrations in the inspired air and in blood must be varied correspondingly to reach the necessary concentration in the central nervous system. Such data for some anesthetic agents at equilibrium are given in Table VII.

As can be seen from the first three columns, there are great quantitative differences between the different anesthetics. Thus the solubility coefficients of ether and nitrous oxide differ by a factor of 30; the oil–water ratio of nitrous oxide and halothane by a factor of 100; and the necessary partial pressure in the inhaled air

TABLE VII

Compilation of Some Biophysical Data on Inhalation Anesthetics

	Solubility coefficient[a]	Oil–water quotient[b]	Partial pressure in the inspired air (%)[c]	Thermodynamic activity[d]
Ether	15	3	3–5	~0.03
Chloroform	7	110	1–1.5	~0.01
Halothane	3.5	330	0.5–2	~0.02
Acetylene	0.8	2.3	70–80	~0.02
Nitrous oxide	0.5	3	80–85	~0.01

[a] Solubility coefficient $= \dfrac{\text{concentration in blood}}{\text{concentration in air}}$

[b] Oil-water quotient $= \dfrac{\text{concentration in oil}}{\text{concentration in water}}$

[c] Partial pressure in the inspired air during anesthetic equilibrium in % of the total pressure.

[d] Thermodynamic activity P/P_0, P = partial pressure of the anesthetic in solution in the brain, P_0 = vapor pressure of the anesthetic in the liquid state at 37°C.

of halothane and nitrous oxide, by a factor of 100. On the other hand, under comparable anesthetic conditions the thermodynamic activities of the individual compounds are nearly identical (column 4). This finding and the absolute value of this quotient indicate with reasonable certainty that the mechanism of action of inhalation anesthetics is of physicochemical character and does not depend on specific interference with cell metabolism.

The table shows further that anesthetics with poor solubility in blood or lipid must be used at a high partial pressure, whereas anesthetics with good solubility can be used at a low partial pressure. The value of the partial pressure and the gradient derived from it determine the rate at which equilibrium between the concentration in blood and the inhaled air is reached. The larger the gradient, the faster the equilibrium is reached, and vice versa. Equilibrium is established within a few minutes for gaseous agents that are poorly soluble in blood, while for easily soluble, vaporized agents, hours may be required. This means that the concentrations of gaseous anesthetics in the inspired air necessary for induction and then maintenance of anesthesia are identical, while vapor anesthetics require a much higher initial pressure to diminish the time that elapses until the necessary blood concentration is achieved. Only then can the partial pressure in the inhaled air be lowered to the value necessary for maintenance of anesthetic equilibrium. The gradient also determines the time required for recovery from anesthesia. The gaseous agents disappear from the blood within minutes (Fig. 50); the same process takes hours for the vaporized agents and cannot, as during induction, be shortened by manipulation of the gradient.

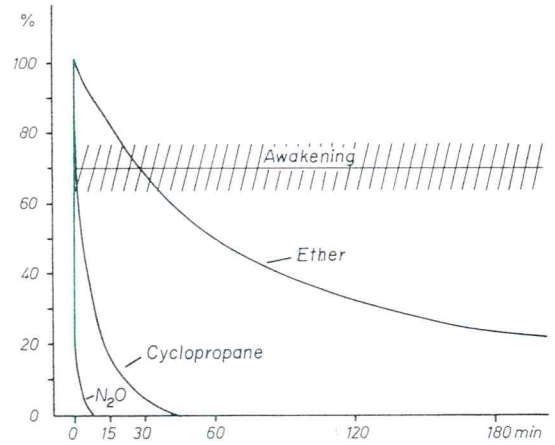


Fig. 50. Recovery from anesthesia with nitrous oxide, cyclopropane, and ether. Abscissa: time in minutes following discontinuance of anesthetic administration. Ordinate: blood concentration; 100% corresponds to the equilibrium concentration of anesthetic during surgical stage. The patient regains consciousness with a concentration between 60–80%. Note the differences between nitrous oxide, cyclopropane, and ether.

Just as any pharmacological agent is characterized by a therapeutic index, so any anesthetic agent has an anesthetic index that is related to the difference between the lethal concentration and the concentration necessary to maintain the stage of surgical anesthesia. Division of the lethal concentration by the concentration required for surgical anesthesia results in a useful ratio for this expression. One should always consider that the anesthetic index of the usual agents is very small—of the order of 1.5, which means that a lethal concentration is reached if the concentration is increased by 50%. By comparison, the approximate therapeutic indices of some other potent pharmacological agents are: morphine, ~ 10; atropine, ~ 200; however, only 2 for digitoxin.

In contemporary practice it is rare to use a single anesthetic agent and the aim is to keep the concentration of any agent as low as possible by means of premedication and combinations of agents. This procedure has decreased the risk in anes-

thesia to such an extent that only one death in 100,000 cases can be blamed on the anesthetic. That number is valid for ideal operative circumstances, which unfortunately are often not fulfilled. The management of the anesthetic, the functioning of the anesthetic apparatus, and the attitude of the personnel attending the anesthesia are not always ideal. Extremely seldom during any form of anesthesia a genetically determined hyperpyrexia can occur (probably together with a myopathy), which usually runs a lethal course.

Ether

Ether is a liquid with a boiling point of 35°C and a specific gravity of about 0.7. Mixtures of ether and air are highly explosive. For anesthetic purposes ether must be highly purified ("ether for anesthesia"). It is available in small containers either of brown glass or metal to hinder the formation of toxic peroxides.

Ether irritates mucous membranes in a concentration-dependent manner. The irritation may cause a reflex cessation of breathing during induction of anesthesia. The secretion of mucus increases throughout the entire respiratory tract. This hypersecretion must be suppressed by premedication with atropine or scopolamine.

Ether is a strong anesthetic; for maintenance of the surgical stage about 3–4% by volume is required in the inhaled air. Reflex activity is markedly inhibited (good muscle relaxation). Vasomotor and respiratory centers are the last functioning brain centers to be inhibited with an overdose. The respiratory center remains unaffected until the middle of the surgical stage. Only a further increase of the ether concentration results in the depressive effect.

The circulatory system, including the heart, is influenced very little by ether. At the beginning of anesthesia the frequency may increase (epinephrine liberation). The blood pressure is normal or slightly elevated during anesthesia. Only in very profound anesthesia does the blood pressure drop owing to a negative inotropic effect on the heart and generalized vasodilatation. The dermal vessels are dilated rather early, elevating the skin temperature. Supraventricular extrasystoles and sinoauricular tachycardia can occur during ether anesthesia, but ventricular arrhythmias are not observed. Moreover, there is no sensitizing effect of ether on the ventricular musculature for the formation of ectopic foci. The effects on myocardial function are very favorable with ether when compared to other anesthetics (chloroform, cyclopropane, halothane).

During ether anesthesia skeletal muscle tone is very low; apart from the inhibition of spinal reflexes, a direct effect of ether on the motor end plate is responsible. Ether has a curarelike effect, and during ether anesthesia lower doses of *d*-tubocurarine suffice to effect neuromuscular blockade than with other anesthetics.

The functions of parenchymatous organs are affected very little by ether. The movements of the gastrointestinal tract and the uterus are inhibited; the metabolic rate is lowered; acid–base equilibrium is not unfavorably affected in the normal course of anesthesia. However, if the oxygen supply and the removal of carbon dioxide are insufficient, acidosis may develop.

Recovery from ether anesthesia is slow (Fig. 50) because of the small gradient between blood and air. During this period, the patient again passes through the excitation stage, with the following frequently occurring symptoms: motor unrest, nausea, and vomiting. These side effects are subjectively very unpleasant and make postoperative care much more difficult. Aside from the irritating effect on mucous membranes and the explosibility, these aftereffects are the only real disadvantages of ether. In contrast, ether possesses some real advantages (relatively low toxicity and ease of application), making ether in combination with atropine a very valuable anesthetic that has not been replaced by newer compounds yet. Contemporary anesthetic practice frequently uses ether in combination with other anesthetics (barbiturates, nitrous oxide, halothane).

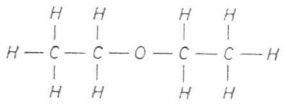
Chloroform

Chloroform is a liquid with a boiling point of 61°–62°C. The necessary concentration in the inhaled air is about 1 volume% at equilibrium, and the lethal concentration is about 1.4 volume%. The anesthetic index is thus very small. Since accidents may occur even with normal concentrations, causing damage to the patient, chloroform has been nearly abandoned. It is not certain whether it is really much more toxic than the very potent agent, halothane, if used expertly with modern equipment.

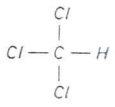
Chloroform depresses the respiratory center; an overdose leads to respiratory paralysis. Even during the surgical stage oxygen tension may be lowered by central depression sufficient to increase the toxicity of the agent. Chloroform is much more toxic to the heart than ether. The negative inotropic effect is marked enough to cause a fall in blood pressure. Moreover, chloroform increases the sensitivity of the heart to epinephrine during the induction of anesthesia; the release of epinephrine at this stage may cause ventricular fibrillation. Furthermore, vagal impulses may be amplified during induction, causing cardiac arrest in extreme cases. Premedication with atropine is therefore necessary. Chloroform inhibits liver function, and very rarely the damage is so extensive that the clinical picture of an acute yellow liver atrophy appears. Probably, the high toxicity can be blamed partly on poor technique (overdosage, lack of oxygen).

Halothane

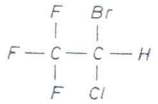
Halothane is a halogen-containing hydrocarbon bearing a physiochemical similarity to chloroform. This highly potent anesthetic has found increasing use for a number of years. It boils at about 50°C and is used with equipment specifically suited to vaporize this compound. Anesthesia occurs relatively quickly, and the onset is subjectively pleasant. The air concentrations necessary to maintain the surgical stage lie between 0.5–1.5% by volume. Recovery is fast and without side effects. Halothane sensitizes the heart to catecholamines in a similar manner to chloroform. Higher concentrations must be avoided since accidental deaths have resulted. The blood pressure is depressed even during the surgical stage, which is attributed to a negative inotropic effect on the heart and vasodilatation, which along with bradycardia occurs through sensitization of the baro-



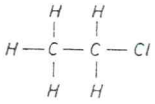
Ether, diethyl ether



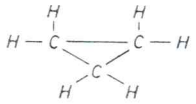
Chloroform, Trichloromethane



Halothane,
2-Bromo-2-chloro-1,1,1-trifluoroethane



Ethylchloride, Monochloroethane



Cyclopropane

receptors in the carotid sinus. Higher concentrations can lead to cardiac arrest or fatal hepatic damage; the latter must be reckoned with after repeated anesthesia with halothane at the usual dose level. It remains uncertain whether or not halothane damages the liver in company with hypoxia, hypercapnia, and hypotonia or whether allergic reactions may be involved as well. Nevertheless, repeated anesthesia with halothane should be avoided, at least within 3 months' time. The analgesic effect is considerably less than that of ether or nitrous oxide. This is one of the reasons why anesthesia with halothane alone should be avoided. It appears to be suitable for use in combination with nitrous oxide or barbiturates in concentrations of 0.5 to 1% by volume.

Methoxyflurane

This close chemical relative of halothane is similar to halothane in its anesthetic properties. Liver damage has not yet been described. On the other hand, reports concerning relatively frequent and long-lasting renal damage call for caution in its use.

Ethyl Chloride

This derivative of ethane boils at 13°C and is kept in pressurized ampules as a liquid. It should not be used as an anesthetic because it is too toxic. However, since the diffusion rate of ethyl chloride is high, a state of stupor and analgesia can be reached in a very short time. Small surgical operations can be quickly undertaken during this state. Even such use is limited because of the danger of cardiac toxicity

(negative inotropic effect and ventricular arrhythmia). Ethyl chloride should no longer be used. Trichloroethylene should be judged similarly to ethyl chloride.

Nitrous Oxide (Laughing Gas, N_2O)

Nitrous oxide is a gas under normal conditions. The highly purified compound is kept liquid in steel cylinders under high pressure, and in such form is available for use in anesthesia. Chemically it is rather inert and therefore presents no explosive danger. It does not undergo any chemical reaction in the organism. Its anesthetic effect therefore is due to physical processes.

The anesthetic potency of nitrous oxide is very low. Even 80% by volume (or volume percent)* in air does not lead to deep anesthesia, although the analgesic effects are relatively strong. The surgical stage cannot be reached without additional measures, and the compound must be combined with other anesthetics or muscle relaxants. An earlier method, involving maintenance of an already initiated anesthesia by means of nitrous oxide, has not found general application.

Loss of consciousness occurs extremely rapidly with nitrous oxide, and the process is reversed very quickly on discontinuing the anesthetic. Vivid hallucinations and dreams may occur during the excitation phase and may appear very real to the patient after awakening; to avoid unjustified accusations against the anesthesiologist, a third person should be present at all times during nitrous oxide anesthesia—and, indeed, during anesthesia with other compounds.

Respiration is not influenced by nitrous oxide as long as enough oxygen is available. The respiratory center can still react to physiological stimuli. The blood pressure remains unchanged if sufficient oxygen is present. However, supraventricular arrhythmias may occur. Other organ systems are not affected by nitrous oxide.

Nitrous oxide is an anesthetic agent with very low toxicity; damage to the patient can occur only if the oxygen level falls below 20% as the result of the concentration of laughing gas being too high. Special care should be taken with older patients suffering from cerebrosclerosis, as even short-term minimal oxygen deficiency can lead to damage of the central nervous system.

While the compound is not sufficiently active alone for surgical anesthesia, its analgesic effects make it ideally suited for combination with other agents, such as ether, halothane, or barbiturates, and even with muscle relaxants. In obstetrics a mixture of 50% nitrous oxide and 50% oxygen provides sufficient analgesia.

Cyclopropane

Cyclopropane is a gaseous anesthetic considerably more active than nitrous oxide or ethylene. Analgesia is induced by 3–5 vol. %; 4–7 vol. % leads to loss of consciousness; and 20–25 vol. % yields surgical anesthesia. Central respiratory depression sets in with concentrations of about 40%. Cyclopropane has two ad-

* All volume percent figures are based on the actual composition of the inhaled air, not on the numbers on an anesthesia machine. For many reasons there may be large differences between the observed and the nominal values.

vantages: (1) the anesthetic index is rather high and (2) the concentrations required allow for a high degree of oxygenation.

The surgical stage of cyclopropane anesthesia is reached more slowly than with nitrous oxide or ethylene (about 5 min); recovery also takes longer (Fig. 50). Nausea and vomiting occur in about 15% of all patients; these side effects are thus much more frequent than with nitrous oxide or ethylene, but occur less often than with ether. In contrast to other gaseous anesthetics, there is a specific influence on the heart. Arrhythmias occur and become more frequent the deeper the anesthesia. This is in contrast to the arrhythmias accompanying ether or chloroform, which occur only during the induction stages. Depending on the depth of anesthesia during the surgical stage, arrhythmias occur with a frequency of 2–10%. The disturbances in the rhythm are mainly of a ventricular nature (ventricular extrasystoles, polytopically induced ventricular tachycardia), and their occurrence indicates the possibility that ventricular fibrillation may develop. The tendency toward ventricular arrhythmias is increased by a number of factors: anoxia, increased carbon dioxide tension, and concomitant administration of catecholamines. During cyclopropane anesthesia sympathomimetic agents should not be given (caution must be exercised with local anesthetics that contain epinephrine or related compounds). The disturbances in cardiac rhythm, if present, disappear when the concentration of cyclopropane in the inhaled air is diminished. They can also be alleviated with β-adrenergic blocking agents. In addition, there is a sensitizing action of cyclopropane on the vagus (sinus bradycardia, partial or total atrioventricular block), which can be suppressed by premedication with atropine.

Mixtures of cyclopropane with air or oxygen are highly explosive, and special precautionary measures must be taken.

Long-lasting anesthesia with cyclopropane alone is relatively seldom performed. The compound is well suited to initiate anesthesia in high-risk surgery and in combination with other agents.

Intravenous Anesthetics

Early experiments to induce anesthesia by intravenous injections of agents such as chloral hydrate, aqueous solutions of ether, chloroform, and magnesium sulfate failed, and only the availability of rapidly eliminated barbiturates made "intravenous anesthesia" possible. In comparison with inhalation anesthetics, intravenous anesthetics have one clear disadvantage: once injected, the dose cannot be modified. The injected quantity can be rendered inactive by elimination and distribution—processes that cannot be influenced by the anesthetist.

Two groups of compounds are suitable for anesthesia by this route: (1) *N*-alkylated barbiturates and thiobarbiturates, and (2) derivatives of phenylacetic acid. As was pointed out earlier during the discussion of the chemistry of barbiturates (cf. p. 160), these barbiturates excel in their rapid onset of action and their high lipid solubility (low degree of dissociation). The *N*-methylated barbiturates are also degraded rapidly in the liver—more rapidly than the thiobarbiturates. The short duration of action is the result of two processes: fast degradation of the compound and redistribution phenomena in the body. The first is responsible for the short

action of *N*-methylated barbiturates (e.g., hexobarbital), while thiobarbiturates leave the central nervous system as the result of their very high lipid solubility without being degraded.

After injection of a thiobarbiturate, a relatively large proportion of the dose enters the brain because of its greater blood flow, while a relatively small fraction enters muscular and fatty tissues, in which circulation is much less. The tissues tend to equilibrate with time, resulting in a redistribution of the drug from the central nervous system mainly to fatty tissues. The concentration in the brain is thus lowered below the anesthetic level without a substantial decrease in the total amount of thiobarbiturate in the body. Experimentally this can be shown very easily. Experimental animals are injected with hexobarbital and thiopental in doses that act for the same length of time. If these injections are repeated at constant intervals, the duration of anesthesia increases every time upon renewed administration of thiobarbiturate. Redistribution is inhibited since the fatty tissues contain considerable amounts of the compound from the previous injections. This effect is not found to any significant extent with the *N*-methylated barbiturates since the duration of anesthesia is determined mainly by degradation.

Since barbiturates and thiobarbiturates are degraded in the liver, although they do not damage this organ, the rate of detoxification is dependent on liver function. Previous liver damage, or hypoxia during anesthesia, decreases the ability of the liver to degrade the compounds. The same dose gives a deeper and longer-lasting anesthesia than in a patient with normal liver function. The use of barbiturates and thiobarbiturates as anesthetics should be carried out more cautiously if liver damage is manifest in a patient.

Sodium Hexobarbital

The solution to be injected must be freshly prepared from an ampule of the dry compound. Of a 10% solution, 0.2–0.4 gm (2–4 ml) are injected slowly (1.0 ml/min) to induce anesthesia. A dose of 1.0 gm (10 ml) should be avoided, even when the

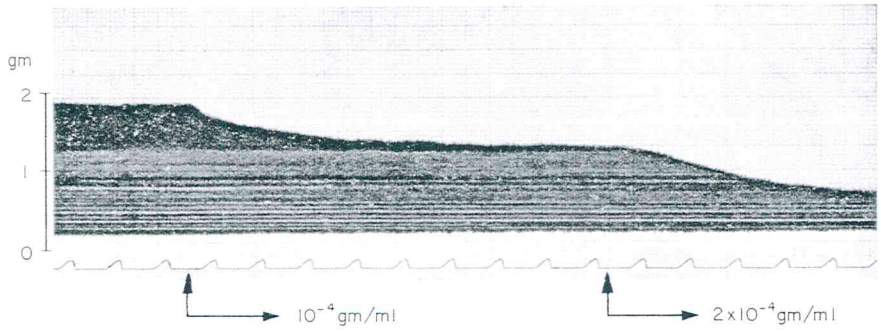


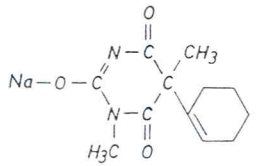
Fig. 51. The effect of hexobarbital on the contractile strength of cardiac muscle. The contraction of an isolated guinea pig atrium is recorded by means of a strain gauge. The time marks on the lower margin are in minutes. At the arrows addition of 10^{-4} or 2×10^{-4} gm/ml of sodium hexobarbital reduces the strength of the contractions in a dose-dependent manner.

total dose is distributed over a longer time. An accidental intraarterial injection of hexobarbital has less disastrous consequences than a similar injection of thiobarbiturate (cf. p. 180).

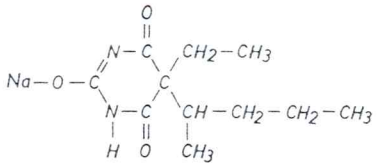
The injection must be made slowly since otherwise the concentration reaching the heart is so high as to diminish contractile force. All barbiturates and thiobarbiturates have a negative inotropic effect. Figure 51 shows an animal experiment illustrating the effect.

The respiratory center is influenced by anesthetic doses of sodium hexobarbital and related compounds (Fig. 49). The respiratory frequency and depth are depressed. Overdoses lead to complete inhibition of the respiratory center (cf. p. 164). Tissue hypoxia considerably increases the toxicity of barbiturates in various organs, especially the liver.

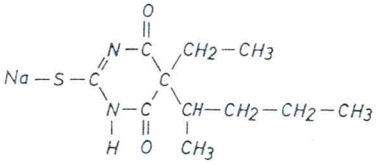
During the induction of and recovery from anesthesia, an excitatory stage may be encountered. Reflex hyperexcitability (especially in the region of the neck, possibly via carotid sinus stimulation) may occur and lead to abnormal vagal



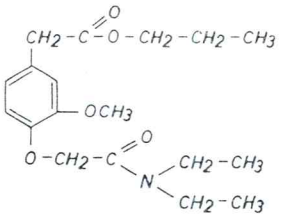
Sodium hexobarbital
5-(1-Cyclohexen-1-yl)-1,5-dimethyl barbituric acid, sodium salt



Sodium pentobarbital
5-Ethyl-5-(1-methylbutyl)-barbituric acid, sodium salt



Sodium thiopental
5-Ethyl-5-(1-methylbutyl)-2-thiobarbiturate, sodium salt



Propanidid
{4-[(Diethylcarbamoyl) methoxy]-3-methoxyphenyl} acetic acid propyl ester

effects on the heart. The hyperexcitability of the vagus is prevented by pretreatment with atropine or scopolamine.

Loss of consciousness occurs very rapidly even with very slow intravenous injection. Subjectively, the patients have only a feeling of going to sleep. They wake again after 10 or 20 min, depending on the dose. Complete motor coordination is not attained for a considerably longer time. Muscular relaxation with hexobarbital anesthesia alone is not well developed; defensive reflexes are inhibited only to a limited extent.

Anesthesia with hexobarbital alone can only be recommended for very short surgical manipulations; the maintenance of longer term anesthesia by constant reinjection of the compound has not been found to be useful. On the other hand, hexobarbital is a very good agent for the induction of anesthesia and for combination with inhalation anesthetics.

An anesthetic agent that must be considered very similar to hexobarbital is sodium pentobarbital, although the duration of action is significantly longer.

Sodium Thiopental

Sodium thiopental in the dry form is available in ampules for the preparation of a 2.5 or 5% solution. To induce anesthesia 0.05–0.1 gm (2–4 ml of a 2.5% solution) must be injected.

Thiopental has essentially the same activity as hexobarbital, but its excretion is somewhat slower (cf. p. 177). Nevertheless, recovery from anesthesia occurs at least as rapidly, possibly even more rapidly, than after hexobarbital. The anesthetic index appears to be somewhat smaller than for hexobarbital. An experimental comparison of the anesthetic indices of these two compounds in the guinea pig is given in Fig. 52. Thiopental and other thiobarbiturates have a greater tissue

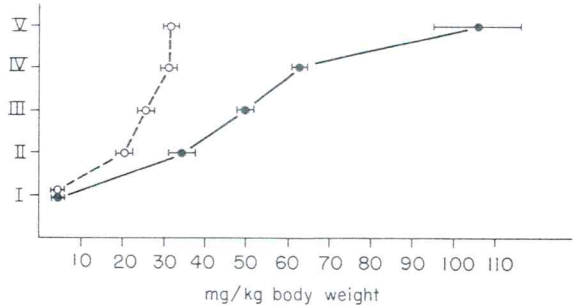


Fig. 52. Experimental determination of the therapeutic index for hexobarbital (—) and thiopental (—) in the guinea pig. The compounds were continuously infused into the animals and the following parameters determined: I, loss of righting reflex; II, disappearance of the Preyer ear reflex; III, loss of the corneal reflex; IV, disappearance of the pinch reflex; and V, respiratory arrest. These points are represented on the ordinate while the abscissa shows the amount per kilogram body weight required to achieve each stage. Each point represents the mean response of 6 animals with the standard error of the mean ($\bar{x} \pm s_{\bar{x}}$). Note the considerably greater therapeutic index of hexobarbital in comparison to that of thiopental. Respiratory arrest occurs simultaneously with disappearance of the pinch reflex with thiopental.

toxicity compared to hexobarbital. Accidental intraarterial injection leads to serious disturbances in blood circulation and to tissue damage, which can lead to loss of the extremity. A specific pharmacological treatment for this local toxic effect is unknown.

Other thiobarbiturates used as short-acting anesthetics are methitural [5-(2-methylthioethyl)-5-(1-methylbutyl)-2-thiobarbituric acid] and thiamylal [5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid].

Propanidid

Propanidid is water-insoluble and is held in solution only with a high concentration of solubilizing agent. For ultrashort anesthesia, 0.5 gm is given intravenously as a 2.5 or 5.0% solution. The compound is primarily degraded by hydrolysis. The time available for the surgical procedure is 2–5 min. From 5 to 7 min after injection the patient is fully awake; after 10–15 min, ambulatory, and after 20–30 min, fully recovered. After an initial period of hyperventilation, respiratory depression is noted for a few minutes. The blood pressure falls transiently, and the heart frequency increases. Occasionally following recovery from anesthesia, disturbances of the autonomic nervous system (vomiting, sweating, and laryngeal spasm) as well as local reactions at the site of injection are observed. Some of these disturbances may be caused by the liberation of histamine, which has been observed in some cases. More frequently involuntary movements occur. At present nothing conclusive can be said with regard to the contraindications.

Anesthetic Premedication

This pretreatment of the patient is done for a number of reasons.

1. The psychological state of a patient soon to undergo surgery is improved by agents that have a sedative and analgesic effect.
2. Induction of anesthesia is made simpler, and less anesthetic is required than without premedication.
3. Suitable premedication suppresses side effects of anesthetics.

Of the large number of drugs that are used for these purposes only the following are mentioned here: sedatives and hypnotics such as diazepam, phenothiazine derivatives and barbiturates; analgesics of the opiate group; and atropine, as a parasympatholytic agent, to prevent dangerous vagal reflexes, or scopolamine, which simultaneously acts as a sedative. Adequate premedication is an integral part of modern anesthesia. It lessens the threat to the patient since less anesthetic can be used. Premedication with diazepam and drugs with similar action changes the patient's sensitivity to muscle relaxants.

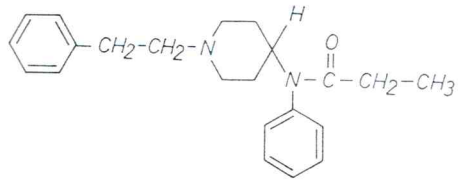
Neuroleptic Analgesia

Neuroleptic analgesia is defined as the condition effected by combined administration of morphinelike analgesics and a major tranquilizer. Such a condition

corresponds roughly to stage 1 of anesthesia; the patient still reacts to stimuli, but there is complete analgesia with subsequent amnesia.

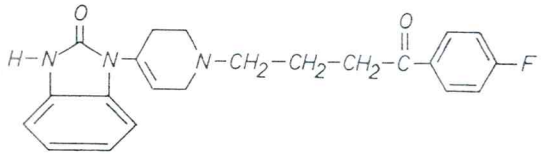
A dose of 60 mg of morphine would produce such analgesia, but the effect would last much too long. Even dextromoramide, the first drug employed for this purpose, has a duration of action of 2–3 hr. At present fentanyl is often used, having an effect lasting for 20–30 min, so that regulation is much easier. The dose for complete analgesia in adults is 0.1 mg, given two or three times intravenously. Like morphine, fentanyl inhibits the respiratory center.

Besides analgesia, a repression of psychic reactions is necessary so that sufficient psychic indifference is produced to allow an operative procedure to be conducted. This is effected with major tranquilizers of the butyrophenone type. Since analgesics can have emetic activity, the antiemetic effect of such compounds is an advantage.



Fentanyl

N-(1-Phenethyl-4-piperidyl) propionanilide



Droperidol

1-{1-[3-(p-Fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl}-2-benzimidazolionen

Every potent major tranquilizer with good antiemetic properties could possibly find use. In practice, the butyrophenone derivatives haloperidol, [1-(3′-*p*-fluorobenzoylpropyl)-4-hydroxy-4-chlorophenylpiperidine], and more recently droperidol are used (about 25 mg intravenously). In contrast to the effect of fentanyl, these tranquilizers have a long-lasting effect which does not completely disappear until 36 hr following administration. With corresponding doses these drugs also are suitable for the usual anesthetic premedication.

The advantage of neuroleptic analgesia lies in the fact that the patient can be questioned during the operation. This is especially valuable in surgery of the brain and inner ear. If these compounds are used as basal anesthetics, low concentrations of nitrous oxide suffice to reach an adequately deep level of anesthesia. The latter combination is especially suited to the patient with cardiovascular disorders and in senility.

In using neuroleptic analgesia it should be noted that the "anesthetic procedure" may involve complete paralysis of the respiratory center, and consequently the availability of the proper anesthetic apparatus is a precondition. It is not a question of the usual, routine procedure and therefore such techniques should be restricted

to special indications in hospitals with very experienced anesthetists. Final judgment of the technique must await further clinical experience.

Antiepileptics

Antiepileptics are agents suitable for the symptomatic therapy of the various forms of epilepsy because they elevate the convulsant threshold without diminishing normal motor excitability. They should possess minimal sedative activity.

The effect of antiepileptics can be demonstrated rather easily in animal experiments. Application of defined pulses of an electric current to the skull of the animal or injection of central nervous system stimulants (e.g., pentylenetetrazole) yield centrally generated motor convulsions, which may be considered equivalent to an epileptic episode. The convulsant threshold of the animal can be considerably increased by pretreatment with antiepileptics; the convulsions may be suppressed completely, or their character altered. Table VIII shows the results of such an experiment performed with mice using an effective antiepileptic agent.

Since epilepsy is a disease that must be continuously treated over decades, antiepileptics require special consideration as far as their therapeutic index is concerned. For this reason only a few compounds have found therapeutic application out of the large number that have shown anticonvulsive properties in animal experiments. Even the best agents in use at present have a low therapeutic index, which in many cases poses a serious problem in achieving sufficient antiepileptic treatment. The choice of drug is considerably determined by the nature of the attack (grand mal, petit mal, etc.) and by the dependence on daily rhythm (epilepsy during sleep, upon awakening, or diffuse), since the antiepileptics exhibit a certain degree of specificity.

Therapy should be initiated with small doses that are slowly increased until freedom from convulsive episodes has been achieved. The exchange of one medication for another should if possible be undertaken in an overlapping fashion. Sudden withdrawal of medication may lead to an acute deterioration in the condition. Every case of status epilepticus must be treated with anesthesia. In addition to

TABLE VIII

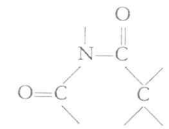
Diminution of the Convulsive Threshold to Electric Shock and Chemical Stimulation in Mice by Pretreatment with Mephenytoin

	Electric shock convulsive threshold for 10 mice (V)	Pentylenetetrazole convulsions (120 mg/kg s.c.)
Controls	48 ± 3	8 out of 10 mice died in convulsions
Mephenytoin (1000 mg/kg p.o. 1 hr before)	73 ± 6	1 out of 10 mice died in convulsions

rapidly acting barbiturates, intravenous diazepam appears to be particularly effective in treating status epilepticus.

A combination of several different antiepileptic agents is frequently a useful therapeutic measure since the beneficial effects are additive while the side effects are different for different agents and not additive. The relationship between doses of the single components must be individually adjusted. Constant medical supervision of the patient is absolutely necessary during treatment with antiepileptics because of the potentially serious side effects. Depending on the specific side effects of the particular drug, blood analyses, urine tests, and liver-function tests should be undertaken routinely. While the serious side effects (blood dyscrasias, liver function disturbances, etc.) compel discontinuance of the treatment, the less serious or transient ones can be treated symptomatically (central stimulants against drowsiness, dark glasses for photophobia, etc.). After administration of antiepileptic agents, the concentration of folic acid in serum and cerebrospinal fluid is diminished. This deficiency, which may cause megaloblastic anemia, has to be compensated for by treatment with folic acid (see also p. 83).

Almost all antiepileptics possess the following chemical grouping:



Only the hydropyrimidine-4,6-dione derivative, primaclone, appears to be an exception. However, this compound is also oxidized in part to a barbiturate in the body. Apart from derivatives of barbituric acid, particularly compounds derived from hydantoin and oxazolidine-2,4-dione are active as are succinimide and acetyl urea derivatives (see the structural formulas). Antiepileptic therapy with bromide ions is now obsolete.

Carbamazepine (5-carbamoyl-5H-dibenz(b,f)-azepine) which chemically is not similar to the antiepileptics (it contains the ring system of imipramine) and is used in trigeminal neuralgia has been advantageously employed in some cases of epilepsy.

It is of note that antiepileptics of different chemical structure can be efficacious in trigeminal neuralgia and migraine.

Barbituric Acid Derivatives

Among the barbiturates, phenobarbital (5-phenyl-5-ethylbarbituric acid) and mephobarbital (1-methyl-5-phenyl-5-ethylbarbituric acid) are best suited for antiepileptic therapy. Mephobarbital has approximately the same anticonvulsant potency as phenobarbital, but its hypnotic activity (a detriment in the treatment of epilepsy) is significantly weaker so that it is generally preferred. The daily dose lies between 0.1 and 0.6 gm. Serious side effects are rare.

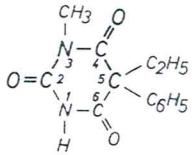
Comparable in its actions to phenobarbital is primidone (5-phenyl-5-ethylhexahydropyrimidine-4,6-dione, deoxyphenobarbital), which must be given in daily doses of 0.5–1.5 gm. Among the side effects, the hypnotic condition predominates, with corresponding psychological complications (giddiness, lack of drive, failure to think clearly, etc.).

The main indication for mephobarbital, phenobarbital, and primidone is grand mal epilepsy; petit mal and psychomotor types respond less well.

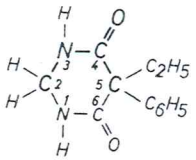
Hydantoin Derivatives

The compounds, diphenylhydantoin (5,5-diphenylhydantoin) and mephenytoin (3-methyl-5-ethyl-5-phenylhydantoin), possess strong anticonvulsive activity without too strongly marked sedative or hypnotic properties. For hydantoin antiepileptics a stabilizing effect on the membrane of peripheral nerves and cardiac muscle can be demonstrated. This finding gives an indication of the mechanism of action of these drugs. The required daily doses are 0.2–0.6 gm although large individual differences in sensitivity exist. Since the action of the hydantoin derivatives is slow in onset, treatment must be undertaken with slowly increasing doses. Along with grand mal epilepsy, the psychomotor type also responds well. A combination of barbituric acid derivatives and hydantoins is frequently suitable for treatment of grand mal epilepsy.

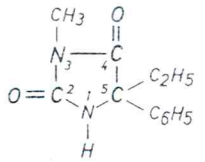
The side effects include drowsiness and psychic disturbances such as confused behavior, depressed moods, and paranoid hallucinations; in addition, drug exanthemas are relatively frequent and sometimes also lupus erythematosus, lymphadenopathy, gastrointestinal disturbances, and hyperkinesis and other neurotoxic symptoms which may be irreversible upon prolonged treatment (ataxia, diplopia). A specific side effect that is observed only on chronic administration of hydantoin derivatives (especially diphenylhydantoin) is gingival hyperplasia.



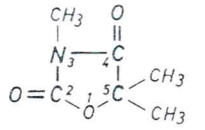
Barbituric acid derivative (e.g., Mephobarbital = 5-Ethyl-1-methyl-5-phenylbarbituric acid)



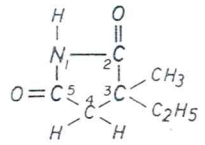
Hydropyrimidine-4,6-dione derivative (e.g., Primaclone = 5-ethyl-dihydro-5-phenyl-4,6(1H,5H)-pyrimidinedione)



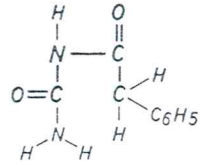
Hydantoin derivative (e.g., Mephenytoin = 5-ethyl-3-methyl-5-phenylhydantoin)



Oxazolidine-2,4-dione derivative (e.g., Trimethadione = 3,5,5-trimethyl-2,4-oxazolidinedione)



Succinimide derivative (e.g., Ethosuximide = 3-ethyl-3-methyl-succinimide)



Acetylurea derivative (e.g., Phenacemide = phenylacetyl urea)

Oxazolidine Derivatives

The compounds trimethadione (3,5,5-trimethyloxazolidine-2,4-dione) and paramethadione (3,5-dimethyl-5-ethyloxazolidine-2,4-dione) are especially active with petit mal epilepsy; grand mal and psychomotor seizures are scarcely influenced. The required daily dose is between 0.9 and 2.4 gm and the institution of therapy with these agents must be undertaken slowly with increasing doses. Tolerable side effects of the oxazolidine series are sleepiness, ataxia, gastric irritation, and nausea. Frequently photophobia occurs with decrease in visual acuity, which may disappear or at least improve with continued therapy. Irreversible damage to visual competence has not been observed. When skin reactions occur, therapy with oxazolidine derivatives must be discontinued. The most serious side effect is damage to the blood-forming bone marrow. Regular blood tests must be taken to detect such toxicity.

Succinimide Derivatives

1-Methyl-4-phenylsuccinimide is effective against petit mal attacks, especially absentia. Ethosuximide is even more useful and leads to freedom from attacks in 50% of all cases of absentia in childhood. Cases of grand mal are not affected; hyperkinesis may be elicited via the striatum.

Phenacemide

Phenacemide (phenylacetylurea) should only be used in cases of epilepsy that are refractory to other medications because the side effects are too severe (toxic psychosis, hepatic and bone marrow damage).

Psychopharmacological Agents

Since ancient times certain agents have been taken by man to achieve psychic effects. Various purposes were intended. The agents were supposed to improve mental or physical abilities, alleviate mental or bodily pain, improve the general disposition, stimulate the imagination, and even elicit hallucinations. Psychological methods have allowed a classification of these agents by group, such as euphorics and eidetics (image formers). An interesting example is a clear account of a deliberately induced reversible psychosis (model psychosis), for example by mescaline, which is derived from a Mexican cactus. On the other hand, all attempts, apart from drug-induced shock, to treat psychoses with drugs were failures until a short time ago; the alternative was placing the patient in an "anesthesialike" state with potent hypnotics.

The new development in psychopharmacology had its beginnings with three pharmacological agents. (1) Meprobamate which in turn was developed from the central muscle relaxant, mephenesin. (2) The second group of compounds was developed on the basis of observed side effects of antihistamines (particularly promethazine) on the central nervous system. The main representative of this group is now chlorpromazine. (3) The third group of agents is represented by the alkaloid, reserpine (from *Rauwolfia serpentina*), which first found use because of its antihypertensive activity. During such therapy the psychotropic effects were noted that led to the use of the compound in psychiatry. The introduction of these agents into medical practice has opened the door to unexpected possibilities in the treatment of psychiatric diseases. A large number of compounds are constantly being synthesized with the aim of surpassing the above agents. The discovery of the hallucinogenic effects of lysergic acid diethylamide, and the isolation of pure psilocybin from Mexican mushrooms which also can generate a "model psychosis," have further stimulated research into the biochemical changes occurring in psychotic states.

Quite apart from the numerous practical successes with modern psychopharmacological drugs, we know very little about the pathogenesis of mental disease and nothing concerning the molecular mechanism of action of the active compounds. However, there now exist series of observations and findings which indicate that at least some mental disorders are linked to disturbances in the metabolism of biogenic amines. In addition, psychopharmacological drugs appear to influence in turn biogenic amine metabolism in the brain. The experimental testing of psychopharmacological agents is done with animals, where the behavior with and without the drugs is recorded as objectively as possible. On the basis of inference to analogous behavior in man, it is hoped that new and better compounds may be found.

Such methods are used, for example, for the following modalities.

1. Motor functions. Spontaneous activity, balance on a rotating cylinder or a tilted floor are tested.

2. Learning ability. With the help of conditioning it is possible to train experimental animals to press a lever to obtain food as a reward only after certain signals. The signals (behavioral cues) can be arranged at different levels of difficulty.

3. Perception and discrimination. These abilities can be tested by means of optical or acoustical signals.

4. Emotion and motivation. Such experiments utilize hunger or thirst to initiate certain behavior patterns. They can also utilize fear and conflict situations (e.g., blowing air on cats or electric shock to rats moving to obtain food). An "experimental neurosis" is created in such a way.

In spite of the extent to which these methods are used, the results of such tests must be considered very critically before they are applied to human behavior. For example, a "sedative" or "tranquilizing" effect in the experimental animals may be the result of nothing other than a muscular paralysis or curarelike action of the test compound. Alternatively, the hunger drive may be disturbed in the animal because of gastritis, general hyperexcitability, or circulatory disturbances resulting from the drug. Drug-induced auditory or visual disturbances may alter the perception of the behavioral cues. In humans, psychotropic drugs are not only used in the therapy of diseases, but attempts are made to obtain a clearer picture of the drug's action by means of psychological tests, tests of motor dexterity, electroencephalograms, questionnaires, etc.

Psychopharmacological nomenclature differs with different authors, and as is generally the case in psychiatry, the number of classifying terms is considerable. Distinctions are drawn between euphorics, psychotomimetics, neuroplegics ("major tranquilizers"), thymoleptics, and tranquilizers ("minor tranquilizers") and psychoanaleptics. The boundaries between these groups cannot be sharply drawn but the classifications are nevertheless useful because of the various indications for use in therapy. In contrast to the antidepressant thymoleptics, the psychoanaleptics have a stimulating effect even on healthy individuals.

The properties of the therapeutically important psychopharmacological drugs are indicated schematically in Fig. 53 in order to give a broad summary of their qualitative activities and indications for use in therapy. A more exact localization of the site of action of a series of centrally acting compounds can already be specified (Table IX).

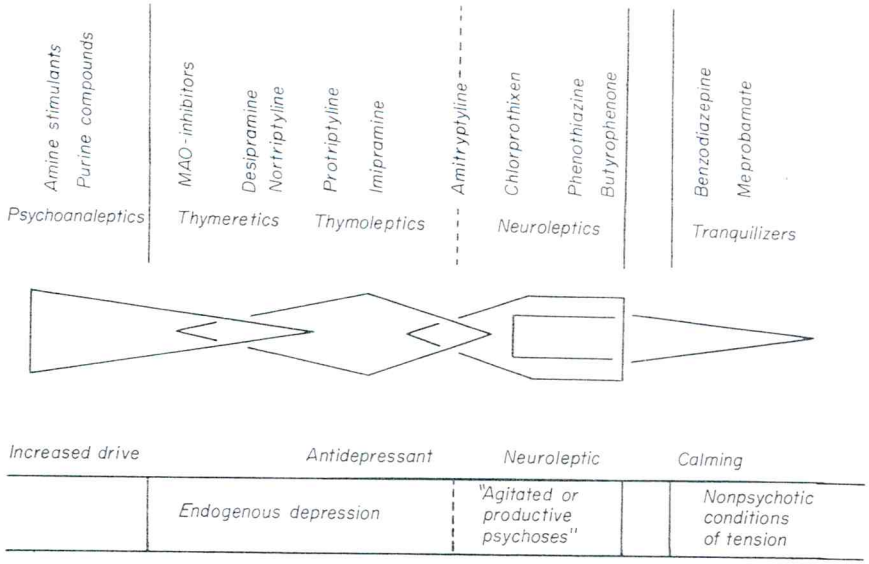


Fig. 53. Schematic indication of the qualitative effects of psychopharmacological agents and indications for their use.

Euphorics

Certain compounds are capable of improving the general disposition of some people. This may lead to a state of euphoria, in which people relish the world and their own existence and in which feelings and thoughts are dominated by enjoyment. It is certainly understandable that people are interested in creating such a condition repeatedly, especially if they are not happy in their lives or are unable

TABLE IX

Representation of Current Notions Concerning the Action of Drugs on Various Functional Units of the Central Nervous System[a]

Compound	"Site of action"[b]				
	Cortex[a]	Thalamus, hypothalamus	Reticular formation	Limbic system	Tectal tracts
Barbiturates	+	+	+	+	∅
Neuroleptics	∅	+	∅	∅	+
Benzodiazepine	∅	∅	∅	+	∅
Meprobamate	∅	+	∅	+	∅

[a] This scheme is for "normal" doses. Following the administration of larger amounts, the function of other regions of the brain is also affected.

[b] + = Inhibition of function; ∅ = no effect.

to cope with their conflicts (neuroses). The "euphorics" (also called intoxicating drugs) that are taken for this purpose may frequently give the desired results, but their use is always accompanied by the danger of habituation (psychological dependence) or even an addiction. This group of compounds not only includes those which eliminate depression and pain (narcotics, opiates) but also those which increase mental or physical activity beyond the normal level.

All over the world, the most frequently used euphoric agent is ethanol. The number of cases of habituation or addiction to alcohol is larger than that for all other drugs combined (concerning the toxicology of ethanol). A very large group, the size of which can only be estimated, consists of those people who are psychologically dependent on hypnotics. Not only barbiturates, but other hypnotic agents are included in this group. Frequently the effect strived for is, again, euphoria. Morphine and morphinelike opiates initially do not always elicit euphoria in healthy persons; frequently the opposite is true. However, repeated administration can also render psychically healthy individuals dependent on these compounds. Cocaine is only rarely used as a euphoric in the form of the pure alkaloid, but the leaves of *Erythroxylon coca*, the plant containing cocaine, are still in widespread use in South America. The amines, amphetamine, methamphetamine, and phenmetrazine have an action similar to cocaine with regard to improved performance, elimination of fatigue, and euphoria. In all cases stimulation of sympathetic centers is involved.

Psychotomimetics

These compounds are also designated as psychosomimetics, psychodysleptics, psychedelics, or hallucinogens. It has been known for a long time that some drugs are able to generate an acute psychoticlike condition in normal persons. The phenomena that occur have great similarity to the symptoms observed in schizophrenic patients. Dissociation, and especially hallucinations, play a role; the compounds have thus quite properly been named hallucinogens.

The symptoms begin a short time after ingestion of the compound and fade away usually after several hours or days. Persons under the influence of psychotomimetics can be a danger to themselves and others. Frequently increased tolerance is exhibited with repeated administration and a psychic but not a physical dependence develops. While the "model psychosis" and endogenous psychosis are not completely identical, it is remarkable that intravenous administration of chlorpromazine quickly abolishes the symptoms of a "psychosis" caused by mescaline. Chlorpromazine is also used as an effective agent in the treatment of endogenous psychosis. The acute "psychosis" elicited by such drugs in healthy individuals should be distinguished from the real psychoses that occur as a result of the chronic abuse of alcohol, sympathomimetic amines, or barbiturates.

Hashish is a resin obtained from *Cannabis sativa* (Indian hemp). It is ingested orally or by smoking cigarettes impregnated with it. Marihuana consists of the dried and cut leaves of the same plant that are also smoked. The most important compound is Δ^9-tetrahydrocannabinol. The abuse of this preparation has consider-

ably increased during the last few years in many countries. After inhalation the effect of hashish is rapid in onset and is stronger than after oral ingestion. After moderate doses the following somatic symptoms are observed in individuals not accustomed to the drug: increase in pulse rate, a reddening of the conjunctiva, dryness of the mouth, nausea. The psychic symptoms are strongly dependent on the personality of the individual, on the surroundings, and on whether the subject is alone or in the company of others. A change in the state of consciousness predominates; the world is misjudged in a dreamlike manner, the estimation of time and space is altered, the lack of coordination of ideas is pronounced. The mood is elevated (euphoria), hallucinations may occur, mimicry and other external expressions seem inappropriate to a person not involved. The effect disappears after a few hours; the drug, however, persists in the body much longer, especially in the brain. Afterward, a depressive mood may appear. After higher doses psychoticlike symptoms such as hallucinations, episodes of fright, and depersonalization occur, and inappropriate or wrong acts with possibly fatal consequences may be carried out (e.g., assuming that one can fly and jumping out of the window).

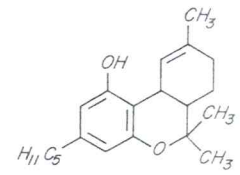
The psychic effect is more pronounced after repeated administration than after the first usage. Since the content of the active compounds varies strongly in the available material, the effect in individual cases, i.e., the intensity of the psychic disturbances, is unpredictable. Upon prolonged consumption of hashish, increasing indolence, lack of productivity, and neglected personal hygiene is possible so that the initiation or performance of social duties becomes impossible. These phenomena occur in young people after a short time, whereas they become evident as a result of chronic alcohol abuse with 10–15 years' latency. Apart from this direct danger involved in the consumption of hashish, an even greater risk is the fact, based on long-term observations, that hashish frequently sets the stage for use of stronger intoxicating drugs like LSD, heroin, and other agents. Accordingly, the prognosis for the treatment of "drug dependence," already unfavorable enough with the chronic abuse of hashish alone, becomes considerably worse. This observation implies that informative and prophylactic influences on prospective users, generally young persons, are of vital importance.

Mescaline is another intoxicant drug with effects similar to those of hashish. The compound is obtained from Mexican cacti (species of *Anahalonium*), and preparations of the drug are used in religious ceremonies. Chemically it is a compound related to norepinephrine but it has only slight circulatory effects. Of note is the occurrence of hallucinations and a split personality. Mescaline is active when ingested by mouth. In some cases abnormal methyl derivatives of biogenic amines possessing mescalinelike activity have been detected in schizophrenics, and therefore have been implicated in a causal manner in the disease.

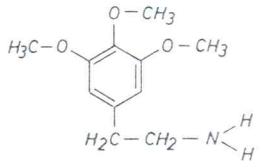
Psilocybin is obtained from Mexican mushrooms. Its effects are similar to those of mescaline, although chemically it is not related to norepinephrine but rather is derived from indole (tryptamine). The substitution in the 4-position is not required for hallucinogenic action, since the introduction of two methyl groups on the amino group of serotonin produces the hallucinogen, bufotenine, which occurs in toad secretions and the seed of a South American plant, *Piptadenia perigrina*. Lysergic acid is a component of all alkaloids from *Secale cornutum*, but it has no

pharmacological effect. On the other hand, lysergic acid diethylamide (LSD), elicits mescalinelike symptoms in man in oral doses of 0.2–0.4 mg. Frequently, however, anxiety and panic reactions occur. As with psilocybin, a 4-substituted indole derivative is responsible (cf. formula, p. 47). It is relatively easily obtained (simple chemical synthesis) so that its misuse is widespread. Although discontinuation of LSD does not result in withdrawal symptoms in the strict sense, in emotionally labile or psychopathic individuals it can lead to changes in conscious-

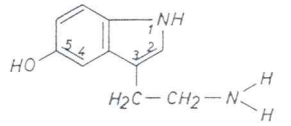
Psychotomimetika



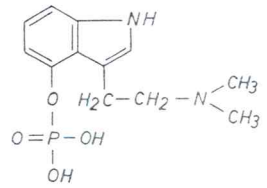
Δ9-Tetrahydrocannabinol



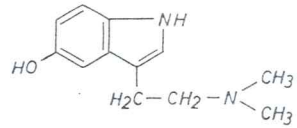
Mescaline
3,4,5-Trimethoxyphenethylamine
(compare to the structure of norepinephrine)



Serotonin
5-Hydroxytryptamine



Psilocybin
Phosphoric acid ester of 4-hydroxy-N', N'-dimethyltryptamine



Bufotenine, dimethylserotonin
5-Hydroxy-N', N'-dimethyltryptamine

ness lasting for weeks even after an interval free of symptoms. It even appears that prolonged psychic damage occurs. In addition, chromosome changes in man have been described.

Neuroleptics, Neuroplegics, Major Tranquilizers

The special feature of neuroplegics (neuroleptics) is that even high doses do not produce anesthesia, while smaller amounts have a marked influence on the psychological state of a psychopathic patient excited by hallucinations and delusions. The result is rest, apathy, and sleep, but not anesthesia; the patient can be aroused. Changes in the electroencephalogram relative to the EEG at rest, which are based on activation of the forebrain by the ascending reticular activating system of the brain stem, can be inhibited by neuroplegics. The depressing influence of the neuroplegics on emotion, psychodynamic state, and basic well-being allows the patient to dissociate himself from his psychotic state and to enter into communication with the physician. A specific therapeutic effect on a particular psychosis is not involved. The treatment is directed not toward specific diseases but toward "target symptoms," such as psychomotor excitation, elevated emotional tension, or psychotic phantasies. The duration of the psychosis is generally not shortened by pharmacotherapy, but the patient becomes more tractable and nursing care is easier. Not only psychic but also somatic manifestations are to be expected with the use of all such drugs. It is not clear if the effects on the body are necessary for the success of antipsychotic therapy.

Neuroleptics and minor tranquilizers influence the reciprocal interactions between the psyche and autonomic nervous system in both psychotic and nonpsychotic individuals. Organs such as the bronchial tree, the gastric mucosa, blood vessels, and the heart, which serve as targets for psychic influence, are "autonomically decentralized" or "psychoautonomically uncoupled" as a result of the drug's effects. Hence, their successful application in disease states with a psychic component such as asthma, ulcers, hypertension, arrhythmias, etc.

The manner in which the neuroplegics interfere with cerebral metabolism is unknown. A large number of investigations have been carried out in order to elucidate the site of action, but have not as yet yielded a satisfactory conception.

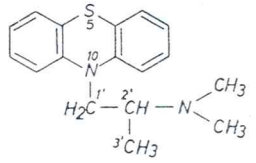
During the treatment of allergic diseases with some antihistamines, side effects were noted in the form of fatigue and depression of the central nervous system. In addition, these compounds augmented considerably the effects of hypnotics and anesthetics. Such effects occurred with antihistamines of the phenothiazine group, such as promethazine. The most important compound and prototype of a whole new group turned out to be chlorpromazine. The molecule consists of a nucleus of three coplanar fused six-membered rings, which is substituted in position 10 with a dimethylaminopropyl side chain and in position 3 with a chlorine atom. While the substitution in position 3 is not absolutely necessary, the side chain occurs again and again in all drugs of this group, either as such or extended with additional substituents attached. If single atoms within the ring system are supplanted by others, the biological effects are changed only superficially or not at all (cf. analog preparations, p. 329). Such a change, however, alters the nomenclature of the ring system. Thus, in the phenothiazine derivative, chlorpromazine, if the nitrogen atom is replaced by carbon in position 10, it becomes a thiaxanthene derivative, i.e., chlorprothixene. If the centrally located sulfur is replaced by two atoms (as in imipramine, cf. formula, p. 194), the ring system loses its flat configuration. It is bent along a medial axis so that the C ring is almost perpendicular to the plane formed by the A and B rings. Interestingly, this compound, which no longer is planar, possesses thymoleptic activity.

Chlorpromazine

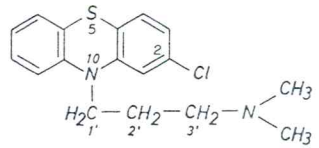
The central depressant and dissociating effect of chlorpromazine, after oral administration of 25–50 mg, reaches a maximum after 1 hr and lasts for about 5 hr. The compound is probably degraded mainly in the liver. Hepatic disease is accompanied by an increase in the sedative effect of chlorpromazine. About 10% is excreted as the sulfoxide in the urine. Aside from those effects that are common to all neuroplegics (sedation, drowsiness), numerous effects of the drug on the central and the autonomic nervous system have been established. It inhibits the functions of the reticular activating system, the thalamus, the area postrema (which can initiate vomiting), and also to some extent the vomiting center. In addition, chlorpromazine has slight anticholinergic, adrenolytic, and antihistaminic activity. The blood pressure is lowered slightly, especially after intramuscular administration. It enhances the effects of numerous central depressants, such as opiates, barbiturates, anesthetic agents, alcohol, and sedatives. Heat regulation is affected probably via an influence on the midbrain. The skin is warm and pale, and the body temperature falls. Hypothermia is easily produced by cooling with ice packs on the skin. Higher than normal environmental temperatures result in a corresponding hyperthermia.

Side Effects

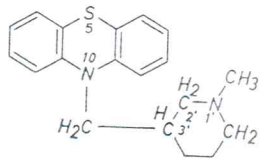
Chlorpromazine applied locally has an anesthetic effect, but it is also a tissue irritant. It should therefore always be given in a highly diluted form and not subcutaneously. The central depressant effects of chlorpromazine may be desirable in outpatients, but more marked effects must be expected when alcohol is ingested at



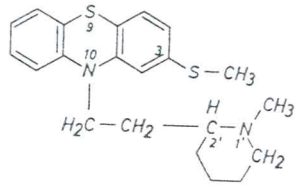
Promethazine
10-(2'-Dimethylaminopropyl) phenothiazine



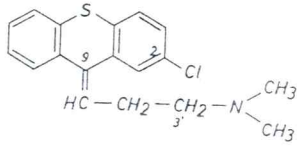
Chlorpromazine
2-Chloro-10-(3-dimethylaminopropyl)-phenothiazine



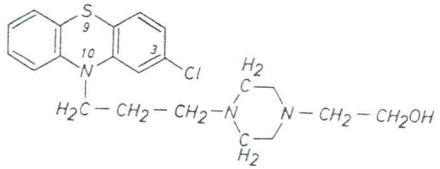
Mepazine (Pecazine)
10-[1'-Methyl-3-piperidyl) methyl] phenothiazine



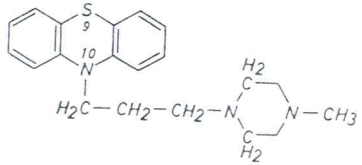
Thioridazine
10-[2-(1-Methyl-2-piperidyl) ethyl]-2-(methylthio)-phenothiazine



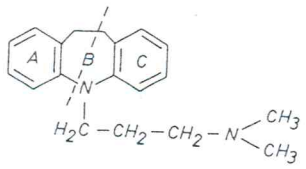
Chlorprothixene
2-Chloro-N,N-dimethylthioxanthene-Δ^{9},-γ-propylamine



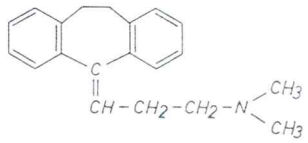
Perphenazine
4-[3-(2-Chlorophenothiazine-10-yl) propyl]-1-piperazineethanol



Perazine
10-[3-(4-Methyl- 1 -piperazinyl)-propyl]-phenothiazine



Imipramine
5-(3 -Dimethylaminopropyl)-10,11 dihydro-5H-dibenz (b,f) azepine



Amitriptyline
10, 11-Dihydro-N,N-dimethyl-5H-dibenzo [a, d]-cycloheptene-Δ^{5},γ-propylamine

the same time or if hypnotics are taken in addition (automobile drivers should be cautious). Following longer use (2–3 weeks), the sedative action can shift to one of excitation. Various allergic skin reactions may occur in about 10%, thrombophlebitis in approximately 3% of all cases. Disturbances in the autonomic system, such as tachycardia in association with hypotension or orthostatic collapse, dryness of the mouth, swelling of nasal membranes, and functional disturbances of the gastrointestinal tract and the bladder frequently have been observed. Signs of Parkinsonism occur after large doses and with frequent administration (cf. p. 129). They generally disappear after the drug is discontinued and as long as they are functional in nature, can be overcome by anti-Parkinson drugs. In certain cases, the Parkinsonism persists after cessation of neuroleptic therapy. Full therapeutic success with neuroleptics is not necessarily connected to the appearance of Parkinsonlike symptoms as a so-called accompanying effect. Disturbances in liver function have been observed in a large number of cases as the result of liver function tests and biopsies. Usually these regress in spite of continued administration of the drug, but in 0.5–1% of the cases cholestatic hepatitis occurs, which is reversed by discontinuing the treatment. Nevertheless, in some patients this condition leads to death, possibly due to previous liver damage. Agranulocytoses are observed in 0.5% of all cases. Rarely edema, convulsions, hypersensitivity to light, hyperpigmentation, gynecomastia in men, menstrual disorders and lactation in women have been described. These disorders may have a similar cause, like the cardiac arrhythmia or "toxic cardiomyopathy" observed in young individuals.

Indications

Chlorpromazine and related compounds have found wide application in psychiatric practice. These drugs have been found especially useful in schizophrenia, manic conditions, and toxic and senile psychoses. The drugs do not cure these mental diseases. Further psychiatric treatment is not made redundant, but the period of hospitalization in many cases has been shortened considerably since these agents were introduced. Daily doses of chlorpromazine are initially 400 mg orally (more rarely intramuscularly) and later 150–300 mg. Chlorpromazine is successfully used as an adjuvant drug in withdrawal therapy for alcoholics and other addicts. In alcoholics the possibility of preexistent liver damage makes the use of related compounds rather than that of chlorpromazine the preferred mode of treatment. Chlorpromazine also has found application in a number of diseases that are not of a psychiatric nature. Examples are anesthetic premedication, vomiting (exclusive of motion sickness), serious hiccoughs and some diseases with contributing psychological factors, such as bronchial asthma, certain circulatory

syndromes, and pruritus. Doses for such indications are 25 mg orally three to four times daily. Only rarely is there any requirement to give chlorpromazine intravenously.

Contraindications

Drugs of this group are contraindicated with liver damage of various causes, as well as in comalike conditions (anesthesia, overdoses of hypnotics).

In order to avoid the danger of orthostatic collapse, the drug should not be given parenterally or in large doses by mouth to outpatients, especially if cerebral or coronary arteriosclerosis is present.

Compounds Related to Chlorpromazine

To gain insight into the effects of the large number of compounds related to chlorpromazine, it is useful to compare them in each case with chlorpromazine itself. Here, as in all other cases, it should be made clear that effectiveness in smaller doses does not necessarily mean that the compound is more effective clinically. In any event, some drugs appear to have better activity against certain "target symptoms." The more apathetic and introverted patients, for instance, are apparently better treated with piperazine-substituted derivatives of chlorpromazine. On the other hand, the drowsiness caused by chlorpromazine and its nonpiperazine derivatives can be desirable in agitated and particularly in elderly psychotic patients.

Among the chlorpromazine-related compounds without a piperazine ring there is promazine which is nearly identical to chlorpromazine; only the chlorine substituent on the phenothiazine ring is missing. The pharmacological effects of the two compounds are comparable, but promazine is less potent and elicits less marked side effects. Liver damage has not yet been described. Mepazine and trifluprom azine are similar to promazine. Thioridazine is similar to chlorpromazine, but extrapyramidal disturbances are rarer. Agranulocytosis and ejaculatory disturbances have been reported. Diminished visual acuity and disturbed night vision have been observed with this and related compounds in some patients after high daily doses (more than 1.6 gm). These phenomena result from usually irreparable damage to the retina, with the symptoms of retinopathy. Thioridazine may eventually be used in internal medicine. In chlorprothixene the nitrogen atom in the phenothiazine ring has been replaced by carbon. The side effects are similar to chlorpromazine. The spectrum of activity contains a certain thymoleptic component.

As neuroleptics and antiemetics, the piperazine-containing derivatives of phenothiazine are active in smaller doses than chlorpromazine or its derivatives. Aggressiveness and hallucinations are depressed. In spite of a general calming effect on the patients, they become less drowsy than after equipotent doses of compounds substituted with nonpiperazine moieties. The antiemetic action includes activity against motion sickness, in contrast to chlorpromazine. Side effects are similar to those of chlorpromazine although somewhat weaker. The development of icterus

is very much rarer. Agranulocytosis has not been observed. On the other hand, extrapyramidal disturbances are more frequent and partly of a different nature than those caused by chlorpromazine—especially after large and moderate doses. Three groups of symptoms occur: (1) A Parkinsonlike syndrome with a masklike face, rigidity, tremor, and salivation. (2) A dyskinetic syndrome that occurs mainly in the head, neck, and shoulder region, including difficulties in speech and swallowing; perioral spasms with protrusion of the tongue, twitching, muscle spasms of the eye, neck, and back, and other muscle groups. (3) Marked motor hyperactivity, constant agitation, restlessness, inability to remain still, or to sleep. These symptoms disappear after discontinuation of the drug or after lowering of the dose. However, cases of irreversible damage are also known. In spite of continued administration, in many cases the very unpleasant side effects can be decreased or eliminated entirely by simultaneous administration of anti-Parkinson drugs (cf. p. 129). Doses of perphenazine in outpatients should not be higher than 12 mg daily orally or rectally. Treatment in a psychiatric ward allows the use of up to 24 mg, if constant medical supervision is assured. The chemical analog, fluphenazine (Cl is replaced by $-CF_3$), should be handled qualitatively like perphenazine. Doses of perazine are higher (two times 50 mg to five times 150 mg daily by mouth).

Numerous additional neuroleptic and antidepressive agents are commercially available, without evidence for their necessity or particular therapeutic value. It is useful to limit oneself to the prescription of a few thoroughly investigated drugs.

Butyrophenone

Haloperidol, droperidol, and other related compounds have potent neuroleptic activity and therefore can be utilized in manic psychotic conditions. They are also used for anesthetic premedication and neuroleptic analgesia (cf. p. 180).

Reserpine

Reserpine is an antisympathetic agent with central and peripheral sites of action (cf. pp. 32, 40). Apart from its chief application in the treatment of hypertension, it was formerly used as a sedative and neuroleptic in conditions of anxiety and tension as well as in chronic psychoses with psychomotor hyperactivity and aggressiveness.

Antidepressants (Thymoleptics)

Drugs with antidepressant activity can be distinguished from the essentially central nervous system-depressant neuroplegic agents of the chlorpromazine group and reserpine. If the effect is primarily an increase in drive or a reduction of inhibitions, the compound is called a thymeretic, while if the activity is more that of lifting of depression or mood elevation, it is designated as a thymoleptic. The thymoleptics can have an especially favorable effect on the basic mood and behavior of de-

pressed patients. They differ from the psychoanaleptics (such as methamphetamine or phenmetrazine) in an analogous fashion as the neuroleptics differ from the hypnotic drugs, i.e., they have no effect on the mood of psychically healthy individuals.

Iminodibenzyl Derivatives and Analogs (Tricyclic Antidepressants)

Imipramine

After an initial depressive phase, imipramine can cause increased drive, especially in a state of anxious depression, but also in other depressions. This effect occurs in the second to third week after the initiation of therapy with a daily dose of 100–200 mg orally. Instead of the sedative effect of neuroplegics, a stimulating effect is noted with imipramine. This compound may also be used in the therapy of nonpsychotic disorders if their origin is primarily in psychic factors. For example, they are successful in the therapy of nocturnal enuresis. Side effects are dose-dependent, and with high doses, frequent. Among these are: atropinelike effects in the mouth, eye, heart, and the gastrointestinal tract as well as states of confusion, occasional hallucinations, sleeplessness, Parkinsonlike phenomena with marked muscle tremor; rarely epileptiform episodes and sudden death from cardiac arrest. Imipramine does not inhibit monamine oxidase. Peripherally, an increase of adrenergic effects is noteworthy along with the atropinelike action. This effect is explained by the fact that imipramine and its metabolic product desipramine (desmethylimipramine), inhibit the uptake of catecholamines into cells. Thus, like cocaine, they elevate the catecholamine concentration in the extracellular space. In contrast to imipramine, desipramine is more active in increasing drive (cf. Fig. 53). Owing to their direct vasodilatory effect imipramine and desipramine reduce blood pressure. As with chlorpromazine, continuous treatment for years may provoke severe damage to the heart. In conditions of acute poisoning cardiac failure has also been observed in children.

3-chlorimipramine and doxepin (one C atom in ring B has been replaced by an O-atom) are analogs of imipramine.

Amitriptyline differs from imipramine in having the ring nitrogen replaced by carbon. The pharmacological actions and side effects are very similar to those of imipramine. Sudden cases of death of cardiac origin have been described. A demethylated derivative, nortriptyline, is commercially available. Protriptyline is identical to nortryptyline except for the double bond between the ring carbon and the first carbon of the side chain. The 3-chloroderivative of imipramine mentioned above acts particularly rapidly and the effect is of short duration. For this reason it can be given intravenously.

Monoamine Oxidase Inhibitors

Several compounds that inhibit (*in vivo* and *in vitro*) the enzyme monoamine oxidase have thymoeretic effects. Their therapeutic value in the treatment of depression is questionable. The enzyme promotes the degradation of biologically important amines, such as norepinephrine and serotonin (5-hydroxytryptamine). Most inhibitors of this group used so far are derivatives of hydrazine, although tryptamine derivatives have a similar effect. The content of norepinephrine and serotonin in various parts of the brain stem is increased after administration of monoamine oxidase inhibitors. The depressant effect of reserpine can be antagonized by these inhibitors in animal experiments. No compound in this group is restricted in its actions to an inhibition of monoamine oxidase since other enzymes are also inhibited simultaneously. It is not possible to attribute a specific therapeutic effect of these compounds to an accumulation of a particular amine in a certain tissue. It is noteworthy that monoamine oxidase inhibitors and imipramine-like drugs interfere with cellular distribution of catecholamines.

Increased activity, improved appetite, a better general disposition, and possibly even euphoria are observed after these drugs in patients with depressed mood. Iproniazid was the first compound of this class but it was used for only a short time since it had serious side effects, in part, life-threatening. Even compounds introduced subsequently which are related to iproniazid, in that they are also hydrazine derivatives, may cause serious side effects. Originally iproniazid was investigated as a tuberculostatic agent because of its relationship to isoniazid. A number of hydrazine compounds were introduced for the same indications and exhibited side effects that were sometimes different but still quite serious, especially in combination with imipramine. Such monoamine oxidase inhibitors are nialamide, phenelzine, isocarboxazide, and tranylcypromine.

Side effects from these hydrazines occur in various organ systems. These are functional disturbances in autonomically innervated organs, such as intestine, bladder, and blood vessels; neurological symptoms, such as paresthesias, retrobulbar neuritis, tremor, and vertigo. Also, jaundice may occur with the symptoms of viral hepatitis and a possible lethal outcome. This was first observed with iproniazid but can apparently occur with any of the hydrazine derivatives in this group. As the result of monoamine oxidase inhibition, certain biogenic amines contained in the diet that are usually metabolized can produce hypertensive crises. Thus, extreme elevation of the blood pressure has been described after ingestion of cheese, certain wines, particularly Chianti, etc. Analogous effects have been observed with the administration of therapeutic amounts of sympathomimetic agents, including L-dopa.

Lithium

The administration of lithium salts has proved to be of value in the therapy of mania in manic-depressive psychosis and for prophylaxis of recurring manic-depressive conditions. The frequency of the phases is reduced. The depressive phase and schizophrenic syndromes are not affected. The manic symptoms are eliminated without impairment of normal psychic function. The patient does not become drowsy. Full activity develops only after daily administration of lithium for 6–10 days. The prophylactic effect against relapses in the disease is observed only after treatment for 6–12 months. The therapeutic index is relatively

small; dosage must be individually adjusted with attention to the therapeutically effective blood level of lithium (0.8–1.2 mEq/liter). Three doses per day of 0.5 gm of lithium acetate is appropriate. Initially half this dose should be used for prophylaxis. The first symptom of overdosage is the appearance of a fine tremor. In addition the following then result: marked trembling, convulsions with corresponding changes in the EEG, muscle weakness, ataxia, dizziness, diarrhea, and polyuria. Death has occurred with overdosing. Cardiac and renal insufficiency, simultaneous sodium restriction in the diet, treatment with saluretic agents or pregnancy are contraindications to the use of lithium salts. Serious intoxications are to be treated by hemodialysis or by forced diuresis.

Minor Tranquilizers (Ataractic Agents)

Minor tranquilizers are designed to moderate states of fear, tension, and compulsion without generating simultaneously the drowsiness caused by sedatives and hypnotics. They should complement psychotherapy, not replace it. In general outpatient clinics it has been shown in many cases that neuroses and states of fear may be treated by placebos with the same degree of success as if tranquilizers were used. The same results can also be achieved by small doses of hypnotics. Tranquilizers are thus not always necessarily better than placebos or hypnotics. On the other hand, they can potentiate the effects of antihistamines, hypnotics, and alcohol. Concomitant use may generate serious hypnotic effects and atactic disturbances. Drivers of cars and people operating machinery can be endangered.

In contrast to neuroplegics, these agents have no influence on psychotic conditions but do inhibit as do the neuroplegics, the influence of the psyche on the autonomic nervous system ("psychoautonomic uncoupling"). Their use is, therefore, indicated in all somatic complaints containing a psychic component. In prescribing tranquilizers and neuroplegics one should always keep in mind that they have psychic effects that are not always the same for a given personality. Decreases in intellectual ability, and drive, flattening of the affect, complete indifference, lowered sensitivity, and decreased responsibility may be expected following long-term administration. In each case it should be considered very carefully whether the existing disease requires such psychological changes and whether they are bought too dearly, particularly since the number of reported cases of addiction has been increasing.

Meprobamate was the first tranquilizer. Many exaggerated expectations were associated with this compound shortly after its introduction. Chemically and pharmacologically it is related to the polyalcohol, mephenesin (cf. p. 128), which was used as a muscle relaxant with its site of action in the spinal cord. Meprobamate has an inhibitory effect on the brain stem, basal ganglia, thalamus, and also on polysynaptic reflexes. It is more potent than mephenesin and its effects last about eight times as long. In experimental animals it antagonizes the convulsant effects of strychnine and pentylenetetrazole. Monkeys treated with meprobamate are reported to lose fear and hostility and to become docile and friendly, while still taking an active interest in their surroundings. In humans a corresponding inhibition of emotional reactions without impairment of manual dexterity and the ability to think and react has been reported.

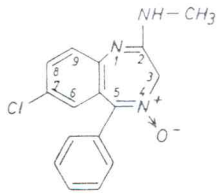
Meprobamate is well absorbed on oral administration; the maximal concentration in the blood is reached after 1–2 hr, and after 24 hr very little is still detectable. About 10% is excreted unchanged. The remainder leaves the body as metabolic products—the glucuronic acid conjugate and the inactive metabolite hydroxymeprobamate. The drug is frequently administered in cases of psychological tension and psychomotor excitation. The oral dose is 0.2 gm three times daily to 0.4 gm four times daily.

Side Effects

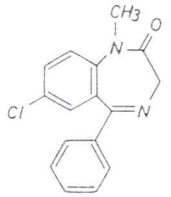
Allergic reactions of various kinds may occur. Large doses cause drowsiness and in some people a depression of their intellectual capability and coordination, especially when the drug is combined with alcohol or hypnotics. In rare cases after long-term administration, habituation and addictionlike conditions have been described. Withdrawal symptoms are sleeplessness, vomiting, anxiety, muscle twitching, and epileptiform convulsions; even fatalities have been reported.

Benzodiazepine Derivatives

Two members of the group of benzodiazepine derivatives with similar pharmacological effects are chlordiazepoxide and diazepam. They have actions similar to those of meprobamate in experimental animals and in humans, but are much more potent. Their site of action in the central nervous system is primarily localized in the limbic system. Wild animals can be tamed by these compounds without influencing their general activity. With repeated doses accumulation must be expected since their complete excretion requires several days. Chlordiazepoxide is given in oral, daily doses of 20–60 mg and diazepam in doses of 4–40 mg to alleviate anxiety and tension in support of psychiatric treatment and for "psychoautonomic uncoupling." The drugs are also used to aid alcoholics and other addicts during withdrawal therapy. In anesthesia premedication, 0.15 mg/kg are given intravenously. The effect of neuromuscular blocking agents of the curare type is then enhanced, whereas that of depolarizing agents like succinylcholine is reduced. Diazepam has a good effect in spastic conditions of various origins, such as tetanus and spastic paraplegia. Unpleasant central nervous system side effects should be watched for carefully, especially in outpatients. In sensitive persons, when high doses are being used, a number of side effects are observed: lassitude and ataxia (especially in combination with alcohol or hypnotics), skin reactions, vertigo, constipation, loss of libido, menstrual disturbances, and increased appetite (possibly with considerable gain of weight). After administration of chlordiazepoxide, agranulocytosis and jaundice have been reported; following diazepam, hallucinations. Similar effects, but primarily hypnotic in nature, are observed with nitrazepam which is closely related chemically. It is used generally as a hypnotic (cf. p. 166).



Chlordiazepoxide
7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide



Diazepam
7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Appendix: Therapeutic Usage of Drugs That Depress the Activity of the Central Nervous System

1. Treatment of nonpsychotic conditions of fear and tension in outpatients. Tranquilizers, hypnotics in low dosage; no neuroplegics.

2. Disturbances of sleep. Hypnotics, eventually tranquilizers; choice of the drug according to the required duration of action (hypnotics that either induce sleep or maintain it).

3. Conditions of severe excitation in psychoses. Neuroplegics, scopolamine, chlorethiazole (especially in delirium tremens).

4. Clinical treatment. In myocardial infarction, diazepam in high doses, no neuroplegics. In hepatic coma, scopolamine. In psychosomatic (psychoautonomic) diseases such as hypertension, bronchial asthma, gastric or duodenal ulcers, ulcerative colitis, etc., tranquilizers, hypnotics and only when necessary neuroplegics for a short time (with caution).

5. Premedication in anesthesia. Neuroplegics, barbiturates, diazepam in high doses, additionally opiates and atropine.

Psychoanaleptics

From the group of nonspecific-acting analeptics, compounds can be selected that primarily influence the psyche. In contrast to the thymoleptics, they are not antipsychotic. They may be grouped under the term psychoanaleptics. Other synonyms are psychostimulants and psychotonics. In overly high doses these drugs, like the analeptics, are convulsants.

Caffeine

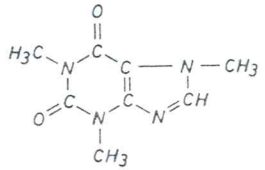
Of the three purines included in this group, caffeine (1,3,7-trimethylxanthine) has the most potent psychoanaleptic effect. Theophylline (1,3-dimethylxanthine) is somewhat less active, and theobromine (3,7-dimethylxanthine) has practically no stimulatory effect on the CNS. Caffeine occurs in a number of plants that have

been ingested as beverages for centuries: *Coffea arabica, Thea sinensis, Cola vera, Ilex paraguayensis* (maté). Caffeine is also synthesized on a large scale to be added to soft drinks.

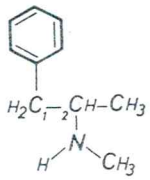
Caffeine acts mainly on the cerebral cortex. Stimulation of autonomic centers occurs only with high doses. Sublethal and lethal quantities of caffeine in animal experiments produce convulsions and excitation of the spinal cord characteristic of analeptics.

The cortical effect of therapeutic oral doses of caffeine (50–200 mg) is dependent on the initial state of the patient; fatigue disappears, alertness and the ability to think are improved. On the other hand, if a person is already wide awake, such an improvement in performance is scarcely noticeable. The doses mentioned above which are contained in 1–2 cups of coffee or tea, make it difficult to sleep or to stay asleep. Caffeine has the paradoxical effect of helping elderly people and sometimes hypertensive individuals to go to sleep. A rational explanation for this effect cannot at present be given. Higher doses elicit disturbed ideation, restlessness, and tremor. The stimulation resulting from normal doses of caffeine is not followed by a compensatory depressed phase. Chronic ingestion of caffeine (drinking of coffee or tea) is not followed by any detectable damage to the individual; only upon the drinking of extreme quantities or in very sensitive persons do restlessness, loss of sleep, and similar symptoms appear. Sudden cessation of its use does not cause any typical withdrawal symptoms.

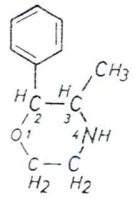
Large doses of caffeine and theophylline stimulate the vascular and respiratory centers. Despite this action, the blood pressure does not increase, since there is also a peripheral action that causes dilation in the vessels of the skin, kidney, and heart. Both compounds promote glycogenolysis by inhibiting phosphodiesterase, which catalyzes the degradation of 3′,5′-AMP (cf. p. 21). Lipolysis is also promoted by 3′,5′-AMP. Noradrenaline is mobilized in the central nervous system and epinephrine in the adrenal glands. Thereby, the aforementioned effects are enhanced. Possibly the cerebral blood vessels are constricted by a direct effect on the smooth muscle (migraine therapy).



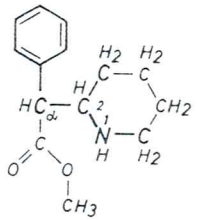
Caffeine
1,3,7-Trimethyaxanthinel



Methamphetamine
d-N,α-Dimethylphenethylamine



Phenmetrazine
3-Methyl-2-phenylmorpholine
(that portion of the molecule resembling methamphetamine is emphasized)



Methylphenidate
α-Phenyl-2-piperidineacetic acid methyl ester
(that portion of the molecule resembling methamphetamine is emphasized)

Caffeine is absorbed quickly and completely from the gastrointestinal tract. Only a small part is excreted unchanged in the urine. The metabolic products result partly from demethylation and partly from oxidation to uric acid derivatives such as 1-methyluric acid, which can ultimately be degraded to urea.

Amphetamine and Methamphetamine

Both amphetamine and methamphetamine are related to epinephrine and belong to the group of sympathomimetic drugs. Apart from a clear peripheral adrenergic effect, these amines stimulate the central nervous system as the result of the fact that in contrast to catecholamines they are capable of penetrating easily into the brain. They release norepinephrine and dopamine from extragranular stores of the adrenergic neurons. There are no differences in the actions of amphetamine and methamphetamine. If the peripheral effects are compared, *d*-amphetamine is more potent than *l*-amphetamine. Propylhexedrine, having a cyclohexane moiety instead of the benzene moiety of methamphetamine, has analogous effects. Coupling of the amphetamine molecule with theophylline yields a compound with central effects, which must be used with the same caution as amphetamine.

In a manner similar to caffeine, the amphetamines are more effective in tired persons than in those wide awake. Fatigue disappears after doses of 3–9 mg, and mood is improved (sometimes leading to euphoria). The functional capacity of the tired individual is restored for a few hours. Whereas there is no objection to the one-time use of amphetamine in an extreme situation, repeated and constant use is dangerous; the individual becomes exhausted due to lack of sleep and food; tolerance develops, requiring an increase in the dose, and eventually habituation and addiction follow.

With addiction the daily dose may rise to 0.5–2.0 gm of amphetamine. Occasionally, toxic psychoses occur, particularly after excessive intravenous doses of this and related compounds. Withdrawal symptoms have been noted.

An additional indication for amphetamine and especially phenmetrazine and phentermine has been propagated under the general term "appetite suppressant." Overweight is nearly always caused by a caloric intake exceeding the daily needs. The only exception is the rare case of a true metabolic abnormality. Correspondingly, loss of weight can only be achieved by a decrease in caloric intake. These compounds indeed suppress the appetite. In addition, they increase the motor activity of the patient and thus the use of calories. The appetite suppressants should thus be considered only as adjuncts to diet control and psychological treatment of obesity. Upon chronic use they lose their activity. The physician should be aware of the disadvantages of these drugs—sleeplessness, increased sympathetic tone, habituation, and the danger of addiction.

Phenmetrazine

The action of phenmetrazine on the central nervous system is comparable to that of amphetamine. The peripheral adrenergic effects are somewhat weaker. The drug has been recommended for a number of indications: as an appetite suppressant, as a mood elevator for depression, as an antidote to the hypnotic side effects of antiepileptics and reserpine. The compound results in habituation and addiction due to its euphorigenic effect. The prescription of phenmetrazine should be undertaken with as much caution as that of amphetamine. In some countries, phenmetrazine has become a frequently used drug of addiction. It should be avoided as an appetite suppressant.

Methylphenidate

In general, methylphenidate has actions similar to those of amphetamine, but the peripheral side effects are less pronounced. It is not suitable for suppressing the appetite. A useful effect has been reported in hyperkinetic children older than 6 years.

Phentermine

In a manner similar to that described above phentermine reduces appetite. Since for closely related drugs serious side effects (pulmonary hypertension) have been reported, phentermine should be given, if at all, with caution; particularly since drug dependency and individual cases of pulmonary hypertension have already been described.

Analeptics

Analeptics are pharmacological agents that in a suitable dosage increase the activity of certain brain centers. In higher doses they are convulsants.

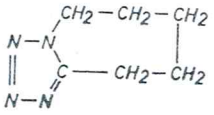
In a strict sense analeptics are called for only in cases of inhibition of the vasomotor or respiratory center that must be overcome for a vital reason. The therapeutic effect of analeptics is entirely central. They have no direct effects on the heart, the blood vessels, or the respiratory muscles. The range of indications for analeptics has decreased considerably with the passage of time. In central vasomotor paralysis the use of circulatory drugs with a peripheral mode of action is now generally preferred; in barbiturate poisoning the use of analeptics has greatly diminished; in opiate poisoning, specific antidotes are available. For managing cases of barbiturate or opiate poisoning, adequate artificial respiration and antibiotic therapy as well as the administration of adequate amounts of water and salts is recommended. If such therapy is not possible, therapy with analeptics can be attempted in order to effect a transient improvement in the patient's condition.

The effects of analeptics can be demonstrated in animal experiments. An example of the reversal of barbiturate-induced respiratory depression is shown in Fig. 49. The convulsions that occur after overdoses of these drugs can also be elicited in animals. Strychnine convulsions are of another type (cf. p. 207). The effects of poisoning are similar in man and animals; the formerly common use of pentylenetetrazole for convulsive therapy of the mentally ill has given rise to a large number of case histories. While experimental results are available concerning the mechanism of action of strychnine, the effects of the other analeptics on a cellular basis are so far unknown.

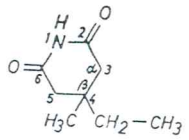
Camphor is the oldest analeptic, but is now obsolete.

Pentylenetetrazole

The following symptoms are observed in normal experimental animals: restlessness, increased motor activity, and increased respiration. Higher doses produce tonic–clonic convulsions that can be lethal because of anoxia if the convulsion is of too long duration, since regular breathing is rendered impossible during such an attack (see Table VIII). The lethal dose is about two to three times the convulsant dose. The stimulating effect of pentylenetetrazole on the respiratory center is best seen in an anesthetized animal, especially if the anesthesia is too deep (see Fig. 49).



Pentylenetetrazole



Bemegride
β-Ethyl-β-methylglutarimide =
4-ethyl-4-methyl-2,6-piperidinedione

Bemegride

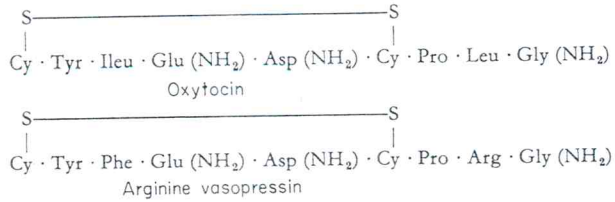
The effect of bemegride is similar to that of pentylenetetrazole. It elicits central excitation with stimulation of the respiratory center; higher doses cause convulsions. The chemical similarity between this compound and the barbiturates (see formulas) gave rise to speculation on a possible specific antagonism between bemegride and the barbiturates. More precise studies have shown that the effect of bemegride is as nonspecific as that of all other analeptics.

Strychnine

Strychnine, occurring in the seeds of *Strychnos nux vomica* is no longer of any therapeutic importance (earlier it was used in tonics or in preparations to overcome sleepiness), but is of particular interest in experimental pharmacology. There also are cases of strychnine poisoning (contracted from rat poisons) that require a specific therapy.

In contrast with the analeptics previously discussed, the main effect of strychnine is on the spinal cord. Moderate doses increase muscle tone (stiff neck muscles) and reflex sensitivity; normal sensory stimuli result in an exaggerated response. The next more severe symptom of poisoning is more marked spreading of reflexes in the spinal cord to the corresponding innervation of large groups of muscles. The next stage is characterized by tonic convulsions initiated by a single stimulus. Poisoning with higher doses (0.03–0.1 gm) results in tetany of all skeletal muscles. Consciousness is retained, and ultimately death is caused by anoxia. The symptoms described above are caused by a marked enhancement of the normal course of events in the normal reflex arc: a single sensory stimulus spreads in the spinal cord and activates far too many motor neurons. The diminished "synaptic resistance" appears to involve disinhibition of interneurons, which are normally under the inhibitory control of Renshaw cells; this inhibitory control is abolished by strychnine. A single dose of strychnine is eliminated completely from the body within 12 hr.

The therapeutic goal in strychnine poisoning must be to suppress the convulsions. The rapidly acting barbiturates (such as hexobarbital) and above all diazepam are useful. The latter compound inhibits polysynaptic reflexes so that the increased distribution of stimuli in the spinal cord is suppressed. All manipulations (such as gastric lavage) must be postponed until the elevated reflex excitability has subsided.



CHAPTER 5

THE ENDOCRINE GLANDS

The endocrine system is remarkably complex in its functions. The secretion of hormones is dependent on a number of factors: the age, sex, and functional state of the organism (disease, pregnancy, psychological influences, drugs, etc.). In addition, there are reciprocal interactions between the individual glands which in part act in the same direction, and in part are interdependent and influence each other by a feedback coupling mechanism. A detailed discussion of the physiology and biochemistry of the endocrine system is not possible here. Three aspects should be considered with regard to endocrine pharmacology and therapy: (1) the use of hormones in deficiency states (substitution therapy), (2) the utilization of specific hormone activity beyond the physiological level, and (3) the influence of pharmacological agents on the synthesis and secretion of hormones.

Pituitary (Hypophysis)

Of the two ontogenetically different parts of the pituitary gland, the anterior lobe occupies a special position since hormones that regulate other glands (organotropic hormones) are synthesized and secreted there. In turn, the formation and secretion of organotropic hormones and also of those hormones that act directly are dependent on specific releasing factors from the median eminence of the tuber cinereum. These "hypothalamic neurohormones" are oligopeptides. Thus the thyrotropin-releasing hormone (TRH) consists of only three amino acids (1-pyroglutamyl-1-histidyl-1-prolineamide). Additional releasing hormones have been discovered for the following hormones of the anterior pituitary gland: corticotropin, the follicle-stimulating and luteinizing hormones, and somatotropin. One can assume

that hormonal and pharmacological activity may be mediated by these factors. Apart from hormones which stimulate the formation or secretion of another hormone in the target organ, the hypophysis also secretes hormones which act directly on tissues: growth hormone, lactogenic hormone, follicle-stimulating hormone, corticotropin with regard to its lipolytic activity, vasopressin, and oxytocin.

The Anterior Lobe of the Pituitary

The hormones of the anterior lobe are polypeptides. The amino acid sequence of the corticotropic hormone has been elucidated. The organotropic hormones are generally species nonspecific, with the exception of growth hormone which is species specific. In contrast to the enormous physiological importance of these compounds, their pharmacological applications are restricted to a small number of indications.

Somatotropic or Growth Hormone (Somatotropin)

Human growth hormone has a molecular weight of 21,500 (188 amino acid residues). It is probably formed in the acidophilic cells of the anterior lobe. Administration of bovine anterior lobe extracts promotes the growth of hypophysectomized rats as well as normal rats above normal. In man these extracts are inactive. Growth responses can be achieved in humans with extracts of human or primate glands. The difference in the effect depends on the difference in the chemical constitution of the polypeptides. Somatotropin deficiency which results in hypopituitary dwarfism can be overcome by weekly injections of 2.5–5.0 mg of human somatotropin. Commercial preparations are not yet available. Apart from its effects on general growth of the body, the hormone stimulates protein deposition and fat degradation. It is an insulin antagonist. This diabetogenic effect was previously attributed to a separate compound. The continued administration of somatotropic hormone stimulates repeated release of insulin from the pancreas so that permanent diabetes mellitus may develop. This is attributable to an exhaustion of Langerhans islet cells.

Thyrotropic Hormone

Thyrotropic hormone is a glycoprotein produced and secreted by the basophilic cells of the anterior lobe which stimulates the activity of the thyroid gland. The exophthalmus-producing factor can be differentiated from this hormone. Experimental and clinical studies have revealed that thyrotropic hormone acts on the following thyroid functions. The uptake and ability to concentrate iodine is increased, thyroid hormones are synthesized more rapidly and secreted in increased amounts, whereby the thyroid epithelium also shows morphological signs of increased activity (high rate of cell division, thickened epithelium, hyperplasia). The secretion of thyrotropic hormone from the anterior lobe of the pituitary is mainly a function of the concentration of the thyroid hormone in the blood. For this

reason, the production and secretion of thyrotropic hormone is diminished or abolished following thyroid hormone administration. Consequently, the thyroid gland becomes quiescent in a morphological and functional sense. On the other hand, the depression of thyroid secretion resulting from partial resection or drug treatment leads to increased secretion of thyrotropic hormone and consequent hyperplasia of the thyroid gland.

Indications for the use of thyrotropic hormone are rare. Sometimes the attempt has been made to improve the uptake of ^{131}I into the thyroid gland in cases of thyroid tumors or metastases of thyroid origin. It can also be advantageously used in ^{131}I thyroid function tests.

Exophthalmus-Producing Factor

This factor is not identical with thyrotropic hormone. A higher blood level can be detected in cases of endocrine opthalmopathy which frequently occurs in hyperthyroidism. Administration of D-thyroxine for a period of months produces a favorable effect on both the blood level of the factor and the exophthalmus.

Corticotropin (ACTH)

Corticotropin (adrenocorticotropic hormone or ACTH) is a polypeptide with a known amino acid sequence of 39 amino acids. ACTH has a specific stimulatory effect on the zona fasciculata of the adrenal cortex, which under the influence of ACTH produces and secretes glucocorticoids, the principal compound in man being hydrocortisone. The extent to which ACTH is secreted, as with other organotropic hormones, depends on the blood level of the hormones of the target organ. In addition it is strongly influenced by psychological and physiological stress (catecholamines). Tetracosactrine, a synthetic polypeptide of only 24 amino acids, is capable of producing corticotropic effects. The adrenal cortical content of cholesterol and ascorbic acid is decreased by corticotropin within a few hours. Biological standardization of ACTH is accomplished by measuring the loss of ascorbic acid from the adrenal cortex of hypophysectomized rats.

ACTH is inactive by mouth, and upon intramuscular injection the effect lasts only a few hours because of its rapid degradation. Various methods have been developed that decrease the rate of absorption from the site of injection; these have led to depot preparations with a duration of action from 12 to 48 hr. Since the only effect of ACTH is to promote the formation and secretion of corticosteroids from the adrenal cortex, the hormone can be used pharmacologically only when the adrenal glands are intact, and not, for example, in Addison's disease.

In all cases in which the adrenal glands are functioning and where glucorticoids are indicated, ACTH can be substituted for the adrenal cortical hormones. A disadvantage in the use of ACTH is the necessity for parenteral administration. For this reason corticosteroids are generally preferred for therapy. The danger of allergic reactions which can occur with ACTH is negligible with the use of tetracosactrine. The recommended adminstration of ACTH upon terminating treatment with glucocorticoids, in order to correct the atrophy of the adrenal cortex that has

developed, is superfluous since the cortex spontaneously resumes its activity. In contrast to hydrocortisone, daily injections of corticotropin do not seem to impair the ability of the adrenal gland to mobilize corticosteroid hormones in situations of stress. ACTH, independently of its effect on the adrenal cortex, influences fat metabolism. It increases lipolysis by activating adenylcyclase. It interacts with the same enzyme as the catecholamines, but the effect is not inhibited by β-receptor-blocking drugs (cf. p. 21).

The daily dose of ACTH is about 40–150 IU intramuscularly given in four to six divided doses. With the depot preparations, the same effect can be achieved with intervals four to six times greater between injections. A dose of 1 mg tetracosactrine gel corresponds to approximately 100 IU.

Gonadotropic Hormones

Three gonadotropins are formed by the anterior lobe, and another by the chorial portion of the placenta. In contrast to some other hypophyseal hormones, the gonadotropins appear to be species specific. They are glycoproteins with a molecular weight of 30,000–100,000. They are inactivated in the blood or excreted in the urine. Biological testing of gonadotropins is performed on hypophysectomized or infantile rats by measurement of the changes in the reproductive organs, the prostate, the vesicular glands, or the uterus.

1. Follicle-stimulating hormone is obtained from horse serum or from "menopausal urine," and stimulates the growth and development of ovarian follicles and spermatogenesis in the testes.
2. Luteinizing or interstitial cell-stimulating hormone causes the secretion of estrogen, ovulation, and the formation of the corpus luteum. In the male, interstitial (Leydig's) cells are stimulated, and the secretion of androgen by these cells is promoted.
3. Prolactin, the lactogenic hormone, achieves the proper conditions for the development of the mammary glands and milk secretion. Other hormones, especially growth hormone, are also necessary. Prolactin is not suitable for increasing acutely the secretion or delivery of milk.
4. Chorionic gonadotropin is obtained from the urine of pregnant women, in which particularly large amounts occur during the first months of pregnancy. It can also be extracted from the serum of pregnant mares. Its effects are similar to those of luteinizing hormone.

Indications

In cryptorchism, if no mechanical obstruction is present, chorionic gonadotropin from the urine of pregnant women or also preparations from the serum of pregnant mares (which contain principally follicle-stimulating hormone) can be very effective. The dose for the first of the above preparations is 100–300 IU daily intramuscularly; for the latter preparation, 1000–5000 IU are given two or three times a week. In cases of primary or secondary amenorrhoea, stimulation of the ovary can be attempted in the following manner: First a series of injections of mare serum gonadotropin to

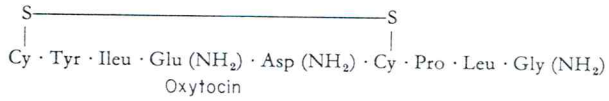
develop the follicle, followed by a second series with chorionic gonadotropin for luteinization. After several such cycles therapy is interrupted in order to establish whether the next cycle occurs spontaneously.

With the administration of a mixture of gonadotropins containing a low content of follicle-stimulating hormone, there is the danger of luteinizing the ovary without the formation of mature follicles. Then ovulation no longer occurs. The same is true if luteotropic or chorionic gonadotropic hormone are administered singly. Extracts of human hypophysis have produced ovulation and the birth of normal children in infertile women, but also frequently result in multiple births and abortions (not a commercial preparation).

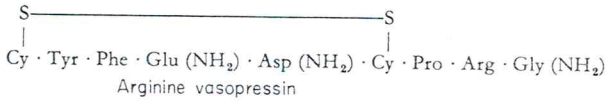
Repeated injection of horse serum gonadotropin leads to the formation of species-specific antibodies, which result in an inactivation of any subsequently administered hormone. In addition, especially when large doses are given, the formation of nonspecies-specific antihormones can occur which inactivate the patient's own anterior lobe hormone. Since this phenomenon only occurs with continuous administration, it is recommended that after 2 weeks of administration the preparation be discontinued for 2 weeks.

Posterior Lobe of the Pituitary

Both hormones of the posterior lobe, oxytocin and vasopressin, are octapeptides which following their formation in the paraventricular and supraoptic nuclei are transported down the supraoptic-hypophyseal tract and stored in the posterior lobe. They can be released from their binding sites in the presence of calcium. These hormones can also be prepared synthetically. Vasopressin is identical with antidiuretic hormone (ADH). Oxytocin has the same structure in all animal species; vasopressin of the pig differs from that of other species in having an arginine residue replaced by lysine.



Oxytocin



Arginine vasopressin

Biological standardization of oxytocin is accomplished with the isolated uterus of the virgin guinea pig. Vasopressin is standardized by measuring its effects on the blood pressure in the dog or cat; its antidiuretic activity by its inhibition of diuresis in the rat or dog. One international unit equals 0.5 mg of the international standard powder and 0.002 mg of pure oxytocin.

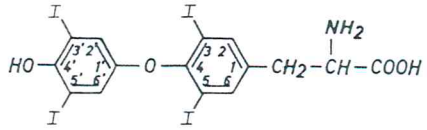
A pharmacological influence on the release of posterior lobe hormones has been demonstrated for some drugs; morphine, barbiturates, and transiently, nicotine stimulate the release of vasopressin from the posterior lobe and thereby inhibit water diuresis. On the other hand, during the period that blood alcohol levels are

increasing, the release of vasopressin is slowed, leading to increased production of urine. The pharmacological effects of oxytocin and vasopressin are discussed in Chapter 1 (cf. pp. 45, 105).

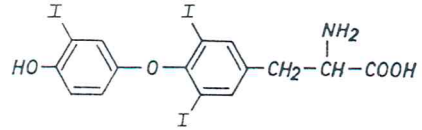
Thyroid Gland

Thyroid Hormones

The thyroid produces the potent hormones, thyroxine and triiodothyronine, along with various iodine-containing compounds which possess no hormonal activity. In the body the two hormones occur only in the optical L-form. The hormone is conjugated with protein (thyroglobulin) in the thyroid follicles. It can be secreted only under the influence of thyrotropic hormone when the bond to the globulin is split by a proteolytic enzyme. In the plasma the hormones are loosely bound again to an α-globulin. The main fraction of the secreted and plasma-bound hormone is thyroxine, while most of the triiodothyronine probably arises from deiodination of thyroxine in the tissues.



Thyroxine
3,5,3',5'-Tetraiodothyronine



Liothyronine
3,5,3'-Triiodothyronine

Pharmacological Effects of Thyroxine

The effects of the thyroid hormones can be deduced from the pathophysiological processes which occur in hypo- and hyperthyroidism. Only the effects that occur after administration of these hormones will be considered here. Thyroxine increases the basal metabolism and metabolic rate. These effects are linked to a loss of weight, increased oxygen consumption, as well as increased production of carbon dioxide. The hormone has a catabolic effect on the metabolism of proteins, carbohydrates, and fats. Liver glycogen decreases, the blood cholesterol level drops, the heart rate increases, and auricular fibrillation may occur. Muscle weakness, nervousness, hyperactivity, tremor, headaches, vasomotor difficulties, and sweating are usual symptoms. Nausea, abdominal pain, and diarrhea occur frequently. The steady strain on the heart may lead to cardiac insufficiency which if accompanied by coronary arteriosclerosis results in symptoms of angina pectoris. Cardiac output and the quantity of urine are increased. The sugar tolerance is lowered, and the sensitivity toward adrenergic compounds enhanced. Oligomenorrhea or amenorrhea may occur.

The mechanism of action of thyroxine has not been fully clarified. The site of action appears to be in the cells themselves, or in the cellular nuclei. Isolated organs from experimental animals which have been pretreated with thyroxine exhibit increased oxygen consumption *in vitro*. High concentrations of thyroxine result in mitochondrial swelling and uncoupling of oxidative phosphorylation. This finding might explain some of the symptoms of thyroxine intoxication. However, it is improbable that this is the basic mechanism of action of the hormone since anabolic processes are involved in its physiological action.

Pharmacological Effects of Triiodothyronine

Qualitatively this compound has the same effects as thyroxine. Its onset of action is much more rapid and the effects wane within a shorter time. Since the compound is also four to five times as potent as thyroxine in influencing metabolism, and conversion of thyroxine to triiodothyronine has been demonstrated to occur in peripheral tissues, it is conjectured that triiodothyronine is the actual active hormone. Although increased oxygen consumption by isolated tissues has not been demonstrated, even with *in vitro* application of triiodothyronine, the other characteristic effects of the thyroid hormones can be elicited by triiodothyronine in isolated cardiac tissue within 20–30 min.

Duration of Action

After intravenous administration of thyroxine in a dose effective in myxedema (5 mg), an effect is only seen after a few days, the maximum being reached after about 9 days. The duration of action is approximately 3–4 weeks, but is dose dependent. After 1 mg of triiodothyronine under similar conditions, the increase in the basal metabolic rate is detectable after just a few hours. The biological half-life of thyroxine is about 6–7 days if the thyroid function is normal. In hyperthyroidism it amounts to 3–4 and in hypothyroidism to 9–10 days. For triiodothyronine the half-life is 1–2 days, depending on the activity of the thyroid gland. In lower doses the onset of action is slower, and the duration shorter.

Indications

These hormones are indicated for substitution therapy in all types of diminished or failing thyroid function. Preparations of desiccated thyroid gland, in oral doses of 0.1–0.3 gm daily are suitable for this purpose. The content of active components in these preparations is standardized so that a uniform level of activity can be expected. The advantage lies in their good activity by the oral route. On the other hand, pure thyroxine loses 60% and pure triiodothyronine about 15% of their parenteral activity when given orally. Due to the long duration of action the danger of cumulation is appreciably greater with desiccated thyroid and thyroxine than with triiodothyronine. Treatment with pure thyroxine is usually unnecessary. If thyroid function is completely absent, daily maintenance doses of between 0.05 and 0.1 mg of triiodothyronine by mouth are necessary; in hypothyroidism, daily doses

of 0.005–0.025 mg are sufficient. In some cases of male sterility an increased number and higher motility of spermatozoa were noted after triiodothyronine (but not after thyroxine). The often-attempted treatment of adipose conditions with thyroid hormone is only appropriate in cases of slight hypothyroidism. It should not be attempted in other cases, because of the ever-present danger of heart damage.

Experiments to utilize the cholesterol lowering effect of thyroid hormones for prophylaxis of arteriosclerosis have not been successful, since frequently attacks of angina pectoris and other cardiac complications occurred. D-Thyroxine is also not suitable for this purpose because of the same side effects. The same holds true for numerous synthetic thyroxine analogs obtained as a result of attempts to produce compounds which maintain the cholesterol-lowering activity without showing the other metabolic effects, particularly on the heart. D-Thyroxine is, however, effective against endocrine exophthalmus (cf. p. 210).

Thyrocalcitonin, a polypeptide of 32 amino acids with a simple chain structure, is a hormone produced in the parafollicular cells of the thyroid. Phylogenetically these cells correspond to the ultimobranchial body in birds, in which the same hormone was found. In man, thyrocalcitonin particularly lowers elevated blood calcium levels and increases the renal excretion of calcium phosphate. It inhibits bone resorption by a direct action. Nevertheless, it seems to be ineffective in human osteoporosis. In animal experiments it has been shown that elevated blood calcium stimulates the secretion of this hormone.

Thyrostatic Agents

Thyrostatic agents or antithyroid compounds are capable of inhibiting the formation of hormones in the thyroid gland, and therefore are suitable for treating a hyperactive thyroid. Compounds from a number of chemical groups have this biological effect, although their mechanism of action may be quite different: (1) iodides, (2) perchlorate and thiocyanate anions, (3) radioactive iodine (^{131}I), and (4) organic sulfur-containing compounds.

Iodides

The effect of iodide ions on the thyroid is not easily understood since it appears to be contradictory. Thyroid function in most healthy individuals is not altered by iodide; however, in some cases, an iodide-induced thyrotoxicosis occurs. With existent exophthalmic goiter (Basedow's disease) the administration of large quantities of iodide effects a considerable transient improvement of the condition within a few days, followed by deterioration. The initial state of the patient appears to be of particular importance for the effect of iodides.

The mechanism of action of iodides has not been explained in detail, but iodides appear to inhibit the mobilization of the thyrotropic hormone from the anterior lobe in much the same way as the iodine-containing thyroid hormones themselves. Since such inhibition cannot be observed with normal thyroid function, it must be assumed that only abnormally increased thyrotropin secretion can be diminished.

Only in quite rare cases following the administration of iodine in doses of more than 5 mg daily over periods of months and years, have goiter and myxedema been observed. Due to the deficiency in thyrotropic hormone during iodide administration, the uptake of iodine into the thyroid gland and the activity of the proteolytic enzyme which releases thyroxine from the thyroid follicle are inhibited. The result is an increased storage of colloid in the thyroid gland.

Indications

Goiter resulting from a dietary lack of iodine can be prevented by administration of iodine salts, such as potassium iodide, in weekly doses of 0.3–1.0 mg. Thyrotoxic symptoms must be eliminated before thyroidectomy. This is accomplished by the administration of potassium iodide solution or Lugol's solution according to Plummer* with daily doses of 50–100 mg of iodine given maximally for 10 days. Iodides must also be given for several days after the operation. If the surgery is not performed, the patient's condition worsens despite continued iodine treatment. These thyrostatic effects of iodide ions can also be elicited with the same advantages and disadvantages by the administration of diiodotyrosine.

Side Effects

After oral administration iodide ions are rapidly and completely absorbed by the small intestine and excreted to a large extent within 12 hr in the urine. Only a small proportion of the dose is retained in the thyroid. After larger doses of iodides, irritant effects on the skin and mucous membranes occur. The symptoms of "iodism" vary individually as far as their intensity is concerned. These include "iodine catarrh," conjunctivitis, bronchitis, and various exanthemas which occur partly as a result of allergic reactions. The effect on the bronchial membranes has led to the use of iodides as expectorants to increase the volume or to liquefy the secretions.

Iodides should not be prescribed when tuberculosis is suspected, since the tuberculous process may be reactivated. Such caution should also be exercised if there is danger of thyrotoxicosis. After administration during pregnancy, goiter and severe hypothyroidism may develop in the newborn.

Thiocyanate and Perchlorate Ions

It has been known for a long time that thiocyanate ions inhibit the uptake of iodide into the thyroid. Thiocyanate apparently displaces iodide. This effect of thiocyanate cannot be used for any therapeutic purpose (although the expected thyrostatic effects set in owing to insufficient supply of iodide to the thyroid) because of an increased tendency toward bleeding that results from prolonged administration of thiocyanate. In rare cases, despite moderate doses of thiocyanate sudden death has resulted. These observations were made when thiocyanate was still used for the symptomatic treatment of vertigo and headaches resulting from hypertension and arteriosclerosis.

* 5% I_2, 10% KI in distilled water.

The perchlorate ion, e.g., potassium perchlorate, also blocks the uptake of iodide by the thyroid gland. Upon constant administration of about 1.6–2.0 gm daily by mouth, distributed over 3–5 single doses, the hyperthyroid basal metabolism falls to normal values within about 4 weeks. Quantities of 0.4–0.8 gm daily suffice for maintenance.

Large amounts of iodide can completely reverse the effect of perchlorate in certain circumstances. On the other hand, the sulfur-containing thyrostatic agents maintain their effect even after administration of iodide since they do not affect the uptake of iodide but rather, inhibit the incorporation of iodine into thyroid hormones. Thus, in this case the quantity of available iodine is of no significance.

Side Effects

The thyroid hyperplasia that may be caused by such therapy can be prevented by the concomitant daily administration of 0.02–0.03 mg of triiodothyronine by mouth. These quantities are sufficient to maintain thyrotropin secretion within the normal range. Allergic skin reactions and very rarely, the sudden occurrence of allergic leukopenia or agranulocytosis have been observed during the first weeks of treatment. This phenomenon should be differentiated from aplastic anemia or panmyelopathy, which slowly develops only after several months of treatment.

Radioactive Iodine (^{131}I)

Radioactive iodine behaves chemically like normally occurring iodine and is excreted to a large extent by the kidney within 1 or 2 days. A residue is stored for a period of time in the thyroid. There ^{131}I destroys the thyroid tissue as a result of its β-radiation. The energy-rich, better penetrating γ-radiation can be utilized to determine transcutaneously the quantity of radioactive material in the thyroid. The physical half-life of ^{131}I is 8 days. Although in principle X-rays can be utilized for the same purpose, ^{131}I allows the application of a larger amount of radiation without the danger of skin damage. The full result of a single dose in thyrotoxicosis occurs after 7–8 weeks. Since the epithelium is largely destroyed, the thyroid becomes smaller. The epithelial cells remaining between the fibrous areas are not normal but still hyperplastic in appearance. Nevertheless with a sufficient dose, the basal metabolic rate becomes normal.

Side Effects

These side effects are similar to those of X-irradiation. Transient inflammation in the area of the thyroid and surrounding tissue occurs. Thyrotoxic symptoms that appear after 4–10 days can be suppressed to some extent by the administration of iodine salts. It should always be kept in mind that genetic damage is possible. After a lengthy latent period thyroid tumors have been found in experimental animals following the administration of high doses of ^{131}I. In man, leukemias have been observed to develop after thyrostatic doses so that this risk should be taken into consideration. In some cases, only years later a hypothyroid condition develops which, however, can be controlled with substitution therapy.

Indications

In hyperthyroidism 1–3 mCi per month should be given orally until the desired effect has been achieved. If angina pectoris is evident in such patients, it can be alleviated with thyrostatic agents, particularly ^{131}I therapy, because the previous imbalance between oxygen availability and consumption is normalized (cf. p. 75). In cases of thyroid tumors, about 250 μCi per gram of estimated glandular tissue are necessary. However, other tissues may be damaged. The marked decrease in the ability of the tumor to take up iodine can be increased with thyrotropin or thyrostatic agents. Metastases take up iodine more readily if the thyroid has been ablated surgically or by radiation. For thyroid diagnostic purposes, only very small quantities such as 30 μCi are administered.

Contraindications

Radioiodine is contraindicated in pregnancy; preferably, it should be used only in people over 40–50 years old.

Sulfur-Containing Thyrostatic Agents

Following the observation that various kinds of cabbage cause goiter in rabbits as a result of their content of sulfur compounds, a systematic search for sulfur-containing thyrostatic agents was instituted. Starting from thiourea, a number of active compounds have been found: methylthiouracil, propylthiouracil, and methimazole.

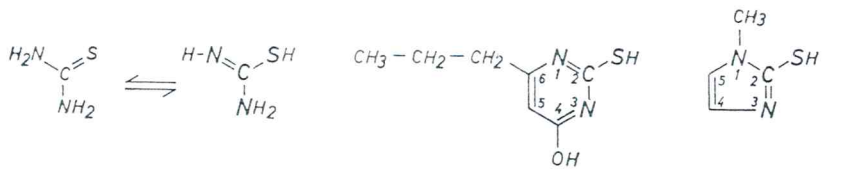
Mechanism of Action

Thyrostatic agents of this group prevent the incorporation of iodide into the amino acids of thyronine. They probably prevent the formation of free iodine by inhibiting the enzymes which oxidize iodide in the thyroid. The uptake and ability to concentrate iodide in the gland are not diminished. There is a latent period dependent upon conditions and dose after the administration of these thyrostatic agents before loss of thyroxine secretion is apparent as measured by the basal metabolic rate and the clinical signs, because the thyroid hormone already present in the thyroid gland and other tissues must first be mobilized slowly. Thyroxine, which normally circulates in the body, constantly inhibits the formation and secretion of thyrotropic hormone. Such inhibition is lost whenever thyroxine production is diminished (iodine deficiency or thyrostatic agents). Owing to the increased secretion of thyrotropin, the thyroid gland becomes hyperplastic and a highly vascularized goiter develops. The ability to take up iodide is increased. With excessively high doses over long periods of time, all the clinical symptoms of myxedema occur.

Side Effects

Apart from the more or less pronounced goiter development, the occurrence of allergies (as well as life-threatening agranulocytosis) must be considered. The number of severe side effects following propylthiouracil and methimazole is around

1–2%; after methylthiouracil, about 10%. Constant attention to the patient's thyroid function and the possible occurrence of side effects (goiter development, aggravation of exophthalmus, bone marrow damage) is necessary. The continued administration of thyrostatics of this group can favor the formation of a thyroid adenoma or carcinoma. This danger is even greater with small doses of radioactive iodine.



Thiourea

Propylthiouracil
2-Thio-4-oxo-6-propyl-1,3-pyrimidine

Methimazole
1-Methylimidazole-2-thiol

Indications

Only if the preferable treatment of hyperthyroidism with radioiodine or perchlorate is not possible should thyrostatic drugs of this type be used. Permanent remissions may develop in about 50% of all treated cases following a period of therapy extending from several months to 3 years. Mild cases should be excluded from such therapy since the results have not been satisfactory. Treatment prior to surgery is not useful because of the vascularization of the goiter. Interference with the development of the goiter can, however, be achieved with doses of desiccated thyroid powder (50 mg daily by mouth). The dose of propylthiouracil is 50–100 mg three to four times daily. Intervals of more than 8 hr between doses should be avoided because of the rapid degradation of the drug. The initial doses of methimazole are 5–10 mg every 8 hr; later, 5–10 mg daily.

These drugs are contraindicated in retrosternal goiter because of the danger of compressing the trachea as the result of the hyperplasia. This is also true during lactation since the drugs pass into the mother's milk and the infant develops symptoms of hypothyroidism. Caution is recommended during pregnancy since with overdoses the new infant can be born with signs of thyroid deficiency.

Parathyroid Glands

Parathyroid Hormones

Extracts from the parathyroids abolish all the symptoms resulting from the removal or destruction of these glands (parathyroid tetany). A polypeptide with a molecular weight of 8600 is responsible for the hormone activity. The hormone is present, according to the sequence of amino acids, in an A, B, and C form. After

parenteral administration of parathyroid hormone, the blood calcium level increases. Consequently, tetany resulting from a depressed level of calcium ions is abolished. The normal calcium level is elevated to supranormal values. Following intravenous injection, about 4 hr are required before the blood calcium begins to increase; the effect lasts for about 20 hr. In bone, the hormone induces an increased resorption of bone substance by osteoclasts. As a result, an elevation in the blood calcium as well as a simultaneous mobilization of phosphate from bone occurs. This hormone directly influences the bone cells since the effect can also be elicited in tissue culture (osteotropic effects). While the calcium levels increase, the blood phosphate falls because the excretion of phosphate is markedly elevated as the result of diminished reabsorption in the kidney. Apparently, this renal effect represents a second site of action of the hormone. The release of the hormone appears to be regulated by the level of calcium in the blood. These or other peptides are possibly responsible for a variety of parathyroid hormone effects since independent effects upon calcium and phosphate absorption in the intestine as well as upon the mammary glands have been found.

Cumulative toxicity of the hormone should be expected after repeated administration of large doses at short intervals. Calcium is deposited in various tissues as the result of the constant supranormal calcium blood values. Blood vessels and the kidney are particularly affected. Death from renal insufficiency can occur with further administration. Hormone overdosage elicits in bone the picture of fibrous osteitis. When parathyroid hormone is given for a long period of time, the effects will diminish (concerning thyrocalcitonin, cf. p. 215).

Indications

Although this hormone when given parenterally is active in cases of hypoparathyroid tetany, the indications for its clinical use are limited. In order to achieve acute effects the intravenous administration of calcium salts is preferred; for prolonged treatment, oral administration of vitamin D_3 or dihydrotachysterol (cf. vitamin D, p. 249) is preferred.

Insulin-Producing Cells of the Pancreas

Insulin

Insulin is produced in the β-cells of the islets of Langerhans of the pancreas and stored in cell granules. It is a hormone consisting of 51 amino acids with a molecular weight of 5734. The small chemical differences between human insulin, pig insulin, and beef insulin are unimportant for the activity of the hormone. They do, however, play a role in immunological responses. The release of insulin from the pancreas is proportional to the blood sugar level. The hormone exists in the free form as well as being bound to β-globulins in the plasma. The half-life of circulating insulin is of the order of 40 min.

Most methods for the determination of insulin in human plasma are not specific. These include, for example, the depression of blood sugar levels in hypophysectomized, adrenalectomized, alloxan-diabetic rats or the uptake of glucose into the isolated rat diaphragm or into the epididymal fat pad of the rat. The radioimmunoassay utilizing iodine-131-labeled beef insulin and an antiinsulin serum of beef insulin obtained from the guinea pig has high specificity. However, proinsulin which is biologically inactive is included in this determination. The usual values found for human plasma insulin range from 60 to 100 microunits per milliliter in the fasting state to 240 to 300 microunits per milliliter in cases of high blood glucose. Various insulin antagonists have been found in plasma. Frequently their levels are elevated in diabetics. Even in the prediabetic and the initial phase of diabetes, levels of insulin and its antagonists are increased in the plasma. In addition, an insulin antagonist has been found in the α_1-globulin fraction which appears during ketosis and then disappears as the ketosis subsides. Considering such observations, it is understandable that the need for insulin can vary markedly. Ketone bodies also have "anti-insulin activity" (cf. below).

Antibodies which appear only after the therapeutic administration of insulin should be differentiated from the above-mentioned antagonists. They are bound to the globulin fraction of the plasma and are responsible for the resistance to insulin in many patients whose plasma binds hundreds of units of insulin. Glucocorticoids can improve this condition apparently through interference with the insulin antibody complex. With the sudden release of insulin, severe hypoglycemia can develop. Allergic reactions (usually at the site of injection) can result from impurities, but also can be in response to the actual active groups of insulin. Since even human insulin can sometimes possess antigenic properties, it is assumed that the tertiary structure of the molecules is changed during isolation.

It is possible to specifically damage the β-cells of the pancreas such that experimental diabetes results. For this purpose alloxan and streptozotocin may be employed. Streptozotocin seems to be useful in the therapy of insulinomas with metastases.

Mechanism of Action of Insulin

Following parenteral administration, insulin lowers the blood sugar level and promotes the synthesis of glycogen, fat, and protein in various tissues. Attempts to relate these various activities to a single basic process have not been convincing so far. An important primary effect of insulin is the increase in the permeability of cells for various sugars. Thereby, the amount of sugar that has penetrated is elevated independent of its further metabolic disposition. The observation that insulin primarily leads to an increase in free glucose but not of hexose phosphates in the cell is contrary to the earlier view that insulin, by activating cellular hexokinase, accelerated phosphorylation of glucose and thus led to the formation of glucose 6-phosphate.

In diabetics, the penetration of glucose into the cell is rendered more difficult as the result of insulin deficiency. Sufficient glucose enters the cell only with an elevated blood sugar level as the result of the larger gradient. Insulin lowers the threshold for the entrance of glucose in a dose-dependent manner. Fat tissue is more important quantitatively in the disturbance of glucose utilization and the development

of hyperglycemia than muscle tissue. Insulin bound to protein is otherwise inactive, but it does stimulate fat synthesis in fat tissues. Glucose uptake into the brain is elevated by insulin.

Normally, amino acids formed as a result of protein breakdown are again incorporated into protein molecules under the influence of insulin. This effect is probably independent of the activity of insulin upon glucose metabolism. In insulin insufficiency, nonutilized amino acids leave the cell and enter into carbohydrate metabolism in the liver. Thereby, additional glucose is produced which is continually given off by the liver into the blood. Insulin stimulates the synthesis of fatty acids from glucose in fat tissue. Fat is continually broken down to fatty acids and glycerine in the fat depots. These acids are continuously resynthesized to triglycerides by esterification with glycerol phosphate. If glucose is not present in the cells in sufficient amounts as the result of insulin insufficiency, the production of glycerol phosphate is depressed, the fatty acids have no reaction partner for triglyceride synthesis, and they leave the fat tissue. In part they are oxidized via acetyl coenzyme A in the liver. In this way the ketone bodies, acetoacetate and β-hydroxybutyric acid, are produced, move into the blood, and are used as a source of energy by muscle or by the brain under starvation conditions. Only with marked insulin insufficiency is pronounced acidosis to be expected as the result of the excess ketone bodies in the blood. Acetoacetate and β-hydroxybutyrate diminish the permeability of cells to sugar. This antiinsulin effect is of no importance in the healthy individual because in compensation larger amounts of insulin are released from the pancreas. On the other hand, in diabetics this effect aggravates the clinical picture and makes the therapy of diabetic coma more difficult.

Indications

Insulin is called for in all cases of diabetes mellitus which cannot be brought under control by diet alone or by oral antidiabetic agents. The dose must be adjusted to the individual case. The daily doses are 20–80 IU subcutaneously; in severe cases from 80 to 200 IU. The effect is seen on the blood sugar within 1 hr and maintained 6–8 hr. In diabetic coma along with glucose, water, and corresponding electrolytes, 50–200 IU is given intravenously and the same dose is administered at the same time intramuscularly. Depending upon the depth of the coma, insulin administration is repeated at short intervals until a total amount of 400–2000 IU has been reached within 24 hr. In very rare cases of marked insulin resistance, extremely high doses must be used. Insulin is not active by the oral route. Depot insulin has the advantage of a longer duration of action but is not appropriate in diabetic coma because of the delayed onset of action. Depot preparations are obtained by combining insulin with zinc, protamine, and globulin. The hormone is so slowly released from these preparations that the duration of action can last from 15 to more than 24 hr.

Side Effects

Allergic reactions are usually locally restricted and often disappear with a change in the preparation. They can be of the "immediate" type as well as the "delayed

type." Excess doses of insulin result in hypoglycemia which leads to weakness, voracious appetite, sleepiness, nervous restlessness, sweating, and trembling. Following higher doses, loss of consciousness, muscle twitching, and convulsions (insulin shock) occur. This dangerous situation can be relieved by the intravenous injection of 5–20 gm of glucose. A dose of 0.4–0.6 mg of epinephrine can be given subcutaneously only if glucose is not immediately available. In such cases the oral administration of sugar is still necessary. In mild cases of hypoglycemia, sugar by mouth is sufficient. Besides serious toxic effects, mild hypoglycemic episodes such as can occur during the night with depot preparations are also of importance. Over a sufficient period of time, damage to the brain or heart can occur in individuals with arteriosclerosis. With insulin treatment of diabetic acidosis, large amounts of potassium pass into the tissues together with sugar. Under certain circumstances life-threatening hypokalemia can develop which is also demonstrable in the electrocardiogram. The *T* wave is depressed or inverted and the *QT* interval prolonged (cf. p. 108). Oral, or if necessary, intravenous administration of potassium salts alleviates this condition.

Glucagon

Glucagon is a polypeptide extractable from the pancreas which consists of 29 amino acids and has a molecular weight of about 3500. Glucagon originates in the α cells of the islets of Langerhans. It elevates the blood sugar as the result of a mobilization of liver glycogen. Even doses of 0.0005 mg/kg intravenously have a demonstrable effect. The biochemical mechanism of action appears to be, as for epinephrine, an activation of phosphorylase by cyclic adenosine monophosphate (cf. p. 21). However, in contrast to epinephrine, glucagon does not act upon skeletal muscle. On the other hand, ergotamine blocks the glycogenolytic activity of epinephrine, but not that of glucagon. It has a weak positive inotropic effect.

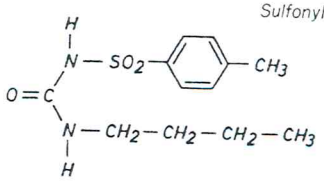
Glucagon is released from the pancreas into the blood and exerts its effects upon the liver; therefore it is considered to be a hormone. Its significance is not yet known. Glucagon has been used clinically in only a few cases, i.e., for the treatment of hypoglycemia following excess doses of insulin; 0.5–1 mg intramuscularly or intravenously was effective. A material with similar, but not identical properties, i.e., enteroglucagon, is released from the intestinal mucous membrane into the blood following food intake.

Oral Antidiabetic Drugs

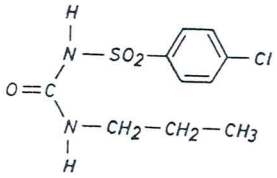
Sulfonylurea Compounds

Following the discovery that the chemotherapeutically active sulfonamides also lower blood sugar levels, there resulted a systematic search for compounds of this group which would be clinically useful in lowering blood sugar. Drugs which are currently used for this purpose are tolbutamide, chlorpropamide, and glibenclamide. Chlorpropamide has a longer duration of action than the other two drugs, although the therapeutic index appears to be smaller.

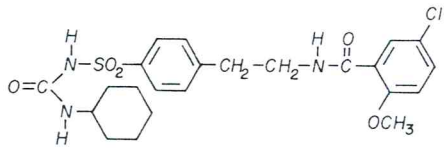
Sulfonylurea derivatives



Tolbutamide
1-Butyl-3-(p-tolylsulfonyl)urea



Chlorpropamide
1-(p-Chlorophenylsulfonyl)-3-propylurea



Glibenclamide
N-4-[β-(5-Chloro-2-methoxy-benzamido)-ethyl]-phenylsulfonyl-N'-cyclohexyl-urea

The mechanism of action of the sulfonylurea derivatives may be explained upon the basis of their ability to diminish the binding of insulin, in which form it is biologically inactive. This release occurs in two places:

1. The pancreas releases more insulin; the insulin content in the blood of the pancreatic-duodenal vein is increased after sulfonylureas. The diminished number of granules in the β cells should be regarded in the same sense since the extent of granulation is proportional to the insulin content.
2. Insulin bound to plasma protein and thereby inactivated (over 50% of the insulin is bound) is released from this binding by sulfonylureas and thereby reactivated.

All of the important effects of these oral antidiabetic drugs are insulin effects; they require the presence of insulin. Individuals devoid of insulin (severe juvenile diabetes mellitus, after pancreatectomy) do not respond to sulfonylureas.

The drugs mentioned above are well absorbed upon oral administration. The individual variation in the rate at which the drug is excreted is considerable. Tolbutamide has a half-life of 4–8 hr; glibenclamide, about 7 hr; and chlorpropamide, about 35 hr. Tolbutamide is largely inactivated by oxidation of the methyl group in the para position. The active and inactive forms of the drugs are excreted by the kidney.

Side Effects

Dermatological or gastrointestinal complaints, intolerance to alcohol, as well as occasional leukopenia, thrombocytopenia, and persistent hypoglycemia with occasional lethal outcome have been observed. Agranulocytosis and cholestatic hepatitis occur very rarely. Additional chemotherapy with sulfonamides increases the level of active compounds in the blood and may cause hypoglycemic shock. Combination with phenylbutazone, salicylates, coumarin derivatives, and probenecid may have similar effects. Protracted hypoglycemia sometimes resulting in death is to be feared, particularly if such combinations are used. Such incidents may also occur after administration of sulfonylurea derivatives alone. The danger is particularly pronounced with compounds having either a long-lasting (chlorpropamide) or more potent effect (glibenclamide). This experience also indicates that an increase in therapeutic activity as measured by the dosage (glibenclamide, 5 mg; tolbutamide, 500 mg) does not necessarily imply an improvement in the therapeutic index.

Secondary Effects

The fear that prolonged treatment with tolbutamide or related compounds might cause exhaustion of the pancreas has not been verified. Such fears were not without reason since other means of stimulating insulin release, such as continuous elevation of the blood sugar level or injections of growth hormone, elicited diabetes in experimental animals. Secondary refractoriness to tolbutamide therapy is to be expected in only 5–10% of the cases which show an initial response. Pancreatic exhaustion could be responsible or it is the result of the continuing progress of the disease. In patients who do not respond in this way, termination of tolbutamide therapy does not change the insulin requirement or the glucose tolerance of the diabetic. Until now an unequivocal answer was not available as to whether therapy with oral antidiabetics prevents the occurrence of secondary disorders to the same degree as does consistent therapy with insulin. Preference should be given to a strict diet together with insulin therapy. Only if the patient refuses insulin therapy or if this treatment cannot be carried out, should the patient be treated with a diet and oral antidiabetic agents.

Indications

Tolbutamide is sufficiently active in daily oral doses of 0.5–1.5 gm in cases of maturity-onset diabetes. Further increase in dose does not lead to a more potent effect. Combination therapy with insulin is senseless. Tolbutamide can be given by intravenous injection to test the functional capacity of the pancreas.

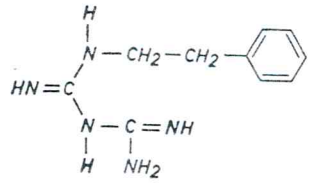
These drugs are contraindicated in juvenile and unstable diabetes, acidoses, precomatose conditions, infections, liver, renal, and thyroid diseases, or during anesthesia, surgery, or pregnancy.

Biguanide Derivatives

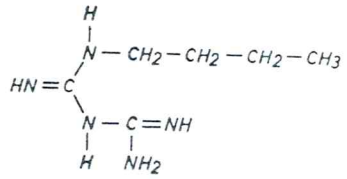
Certain biguanide derivatives (phenformin and buformin) have a mechanism of action different from that of tolbutamide. In the first few hours following oral administration, the blood sugar level falls. The effect lasts from 6 to 14 hr. In contrast to the sulfonylurea derivatives, this effect can be enhanced by an increase in

the dose. However, such an increase in dose is limited by the appearance of marked side effects in the gastrointestinal tract. All diabetics, but not healthy individuals, react to these drugs with a lowering of the blood sugar. The mechanism of action is

Biguanide derivatives



Phenformin
1-Phenethylbiguanide



Buformin
1-Butylbiguanide

not known. The presence of endogenous or exogenous insulin is necessary for activity which appears to occur only in the skeletal musculature. It is possible that the anaerobic metabolism of glucose is stimulated. With respect to the desired effect, it is important that the drug diminishes the intestinal absorption of food components, although probably not that of protein. Accordingly, considerable loss of weight occurs in obese diabetics, which is doubtlessly favorable. As a result of intestinal irritation, appetite is generally reduced, a phenomenon which certainly contributes to the therapeutically desirable loss in body weight.

Indications

Diabetics who respond to sulfonylurea compounds should not receive biguanide derivatives since the frequency of side effects (serious gastrointestinal disorders, particularly nausea and vomiting) restricts or prohibits their use. Whether these drugs have a further favorable metabolic influence apart from the lowering of blood sugar is currently unknown. They should be used only in exceptional cases. The daily dose of buformin is about 150–300 mg by mouth.

Steroid Hormones

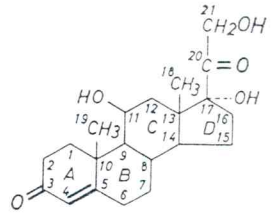
The hormones from the adrenal cortex and the gonads constitute the steroid hormones. Their chemical structure is based on that of cyclopentanoperhydrophenanthrene which also occurs in the cardiac glycoside molecule. Whereas the

latter requires ring fusions of AB cis, BC trans, and CD cis to have cardiotonic activity, the steroid hormones have their rings fused AB cis, BC trans, and CD trans.

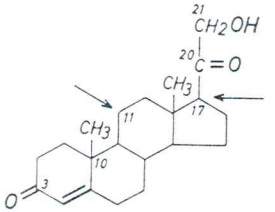
The steroid hormones can be divided into four functional groups. Each of these groups has certain molecular structural characteristics (see the formulas).

1. Corticosteroids: A double bond in ring A, which is conjugated with the carbonyl function at C-3; also, a carbon side chain on ring D (C-17), which contains a carbonyl oxygen at C-20 and a hydroxyl group at C-21. The glucocorticoids have more hydroxyl groups (e.g., at C-11 and C-17) than the mineralocorticoids.

Corticosteroids

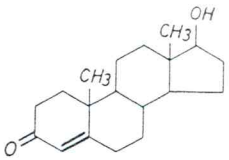


Hydrocortisone
(Glucocorticoid)



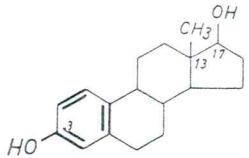
11-Deoxycorticosterone
(mineralocorticoid)
Arrows indicate the differences compared to glucocorticoids

Androgen

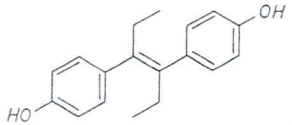


Testosterone

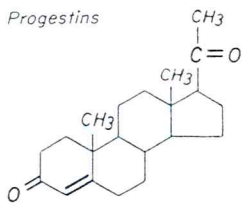
Estrogens



Estradiol-17β



Diethylstilbesterol
(synthetic!)



Progesterone
(Note similiarity to 11-deoxycorticosterone)

2. Androgens: A conjugated double bond in ring A and a carbonyl oxygen at C-3. Carbon 17 carries only a hydroxyl group. The androgens differ from the estrogens by a methyl group at C-10 and a higher degree of saturation in ring A.

3. Estrogens: Ring A is aromatic and has a phenolic hydroxyl group at C-3, a hydroxyl group is present at C-17, and a methyl group at C-13. The synthetic stilbene derivatives with estrogenic effects simulate this pattern to a large extent.

4. Progestins: Again, a double bond in ring A conjugated with a carbonyl group at C-3. In addition there is a carbon chain at C-17 that contains a carbonyl oxygen at C-20, but does not have the neighboring hydroxyl group at C-21 as in the corticosteroids.

Adrenal Cortex

A series of corticosteroids can be isolated from the adrenal cortex which are chemically related but have different physiological and pharmacological effects. Certain of these steroids have estrogenic or androgenic properties and with pathological changes of cortical function large quantities of androgens or estrogens may be released. On the other hand, progesterone has certain corticosteroidlike effects. The corticosteroids can be divided into two groups, the glucocorticoids and the mineralocorticoids, according to their physiological or pharmacological effects. The naturally occurring glucocorticoids are formed in the zona fasciculata, the mineralocorticoids in the zona glomerulosa, and the androgens in the zona reticularis.

Glucocorticoids

Glucocorticoids are chemically derived from Δ^4-pregnene and carry keto groups at C-3 and C-20 as does progesterone. The introduction of hydroxyl groups into C-11, C-17, and C-21 yields hydrocortisone which in humans is the principal compound with glucocorticoid activity secreted into the venous blood by the adrenal gland. If the hydroxyl group at C-11 is oxidized to a keto group, the resulting compound is called cortisone. The introduction of a second double bond into ring A converts hydrocortisone to prednisolone and cortisone to prednisone (cf. p. 232).

All of these glucocorticoids also have mineralocorticoid activity, which can be

increased by the introduction of a fluorine atom in position C-9. However, if at the same time a methyl group is introduced in the 16α-position as in dexamethasone, or a hydroxyl group as in triamcinolone, the mineralocorticoid activity is lost while the glucocorticoid activity is almost entirely retained.

The secretion of hydrocortisone is stimulated by corticotropin (ACTH) from the anterior lobe of the pituitary. This is the result of a direct effect since it can also be detected in isolated perfused adrenal glands. Apart from physiological basal secretion, the increase in corticotropin release with corresponding elevation of hydrocortisone secretion plays a particular role in stress situations. Under normal circumstances almost 95% of the hydrocortisone is bound to transcortin, an α-globulin. Only the unbound, free fraction is biologically active. The binding capacity is about 20 μg % and can be exceeded by the administration of glucocorticoids. The hydrocortisone not bound to transcortin is rapidly degraded; the half-life for this process is approximately 80–150 min in healthy individuals.

Pharmacological Effects of Hydrocortisone (Cortisol)

Hydrocortisone is essential to life; its complete absence as the result of disease or adrenalectomy results in death within a few days. Hydrocortisone or a similarly acting drug must be administered in order to cause the disappearance of the symptoms of deficiency which are characterized as Addison's disease. In such substitution therapy, hydrocortisone alone or in combination with a mineralocorticoid relieves all of the symptoms of Addison's disease. In addition to such therapeutic use, glucocorticoids have special pharmacodynamic effects which can be utilized therapeutically.

Hydrocortisone inhibits glucose utilization in peripheral tissues and increases gluconeogenesis from amino acids. Protein synthesis is diminished in this way and the overall result is a decrease in body protein (protein catabolic effect). As a result, body growth is also diminished. The blood sugar level (with possible glucosuria) and hepatic glycogen synthesis are elevated because of the increased gluconeogenesis. These changes in carbohydrate metabolism correspond in some ways to those of insulin deficiency. Therefore, it is understandable that experimentally induced diabetes mellitus is improved by removal of the adrenals. The change in fat metabolism whereby the deposition and distribution of body fat are abnormal (moon face, buffalo hump) is not yet understood in terms of its mechanism.

Electrolyte and water balance are affected by hydrocortisone to a lesser extent than by mineralocorticoids. However, this side effect can be dangerous upon long-term administration; hypokalemic alkalosis can develop as the result of sodium retention and increased potassium excretion. Water is retained simultaneously with the sodium ions. The mechanism of action with regard to electrolyte balance is the same as that of mineralocorticoids. On the other hand, the deterioration in the capacity to excrete water which accompanies deficient adrenal function can be abolished by adminstration of hydrocortisone.

Hydrocortisone inhibits the activity of lymphatic tissue. Lymphopenia and shrinking of the lymph nodes is the result. The thymus, which is important for the formation of specific proteins in the individual, atrophies after long-term

administration. Similarly, antibody formation and antigen-antibody reactions are reduced following high doses. Hydrocortisone also inhibits growth and all reactions of the mesenchymal system. The release of cytotoxic enzymes from intracellular lysosomes during infections is also impaired. The simultaneous elevation of fibrinolytic activity and the decrease in plasma fibrinogen may play a role in the anti-inflammatory and antirheumatic effects. These antiinflammatory, antiallergic, and antirheumatic effects of hydrocortisone and other glucocorticoids are the important ones for pharmacotherapy. The further mechanisms responsible for these effects have not been clarified. It is noteworthy that glucocorticoids inhibit the biosynthesis of acid mucopolysaccharides. This can be measured as a reduction in the uptake of ^{35}S in tissues.

Methods for Evaluating Antiinflammatory Agents

In order to measure antiinflammatory activity, a reproducible inflammation in experimental animals must be produced and the degree of the inflammation quantitatively evaluated on the basis of various measurements. The regression of these inflammatory signs is then quantitatively judged on the basis of changes in these measurements under the influence of antiinflammatory drugs. Among others, the following methods have been used.

1. Evaluation of an erythema by means of a photometer or by measurement of skin temperature. This method is also used with humans.
2. Measurement of the permeability of skin capillaries or the synovial membrane to a dye. The appearance of the dye in the inflamed area (skin or joint) is determined.
3. Measurement of the edema produced by injection of an inflammatory agent (i.e., formalin or dextran) in the rat paw. The volume of the rat paw is determined.
4. Measurement of the granuloma that occurs upon injection of the strong local irritant, croton oil, into an air-filled, subcutaneous pouch in the rat.

The variety of such tests demonstrates the complex series of events involved in the production of experimental inflammation and also the difficulty of evaluating the clinical usefulness of drugs from the results of such single tests.

Side Effects of Glucocorticoids

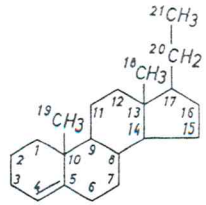
The inhibition of mesenchymal reactions by glucocorticoids hastens the progress of some diseases. The formation of granular and scar tissue can be considerably retarded. Gastrointestinal ulcers can be formed or reactivated, particularly since the acid production of the stomach is usually elevated. Infections spread more readily or clinically manifest themselves for the first time (tuberculosis). Necrosis of the pancreas has been reported. The following symptoms, similar to those of Cushing's syndrome, can occur with long-term administration; increase in appetite and body weight, abnormal distribution of fat (moon face, buffalo hump) sodium and water retention ultimately leading to edema and hypertension, glucosuria, glaucoma, hypokalemia, hypertrichosis with loss of hair, acne, skin pigmentation, striae,

cutaneous bleeding, thrombophlebitis, negative nitrogen balance, and intestinal loss of calcium accompanied by osteoporosis which can result in spontaneous fractures. Fluorinated steroids can lead to morphologically demonstrable changes in skeletal muscle and corresponding muscle weakness. The mood is usually elevated with glucocorticoid therapy; or it can result in euphoria which leads to habituation and addiction. Psychosis as well as convulsive episodes in children have been reported.

Glucocorticoids inhibit the secretion of corticotropic hormone. As a result the adrenals atrophy. A threatening condition of shock can occur with the sudden withdrawal of glucocorticoids, if the patient is subjected to stress. In order to avoid such a situation, glucocorticoids should be withdrawn gradually. Cortical atrophy is reversed within days or weeks following discontinuance of glucocorticoids. (Concerning the prevention of cortical atrophy by corticotropin injections, see p. 210). On the other hand, the administration of a daily dose of 20 to even 50 mg prednisone early in the morning does not seem to impair the circadian rhythm in the secretion of corticotropin and hydrocortisone.

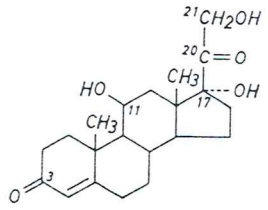
Differences in the Action of Various Glucocorticoids

A comparison of the effects of hydrocortisone with those of related compounds having qualitatively identical antiinflammatory activity reveals the following differences: cortisone, which today is hardly ever used, is about 20% less potent; prednisone and prednisolone are 4 times, triamcinolone 5 times, and dexamethasone about 25 times as potent. The same relationship holds for the antirheumatic and antiallergic effects, the negative effects on nitrogen and calcium balance, the changes in carbohydrate metabolism, and the production of atrophy of the adrenal cortex. The retention of sodium and loss of potassium are less following prednisone and prednisolone than after hydrocortisone but nevertheless significant upon prolonged administration. Sodium and potassium balances are only slightly affected after triamcinolone and dexamethasone. For this reason these compounds are not suitable for the treatment of adrenal cortical insufficiency since simultaneous administration of a mineralocorticoid would be necessary. Both drugs under certain circumstances elicit an increasing muscle weakness in the presence of normal potassium blood levels. This is a disquieting symptom that is perhaps the result of damage to the muscle fiber. Dexamethasone has little and triamcinolone no euphorigenic effect. The latter, in contrast to the other glucocorticoids, diminishes the appetite.

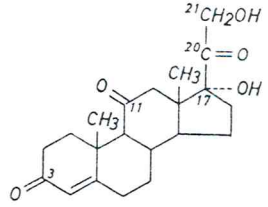


4-Pregnene

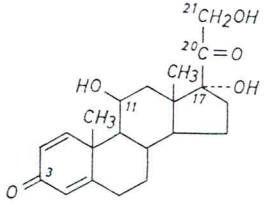
The α-configuration is represented by dotted lines and the β-configuration with solid line in the formulas.



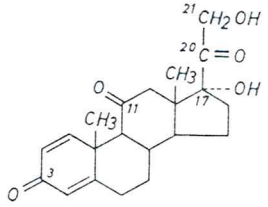
Hydrocortisone, cortisol
11β,17α,21-Trihydroxy-4-pregnene-3,20-dione



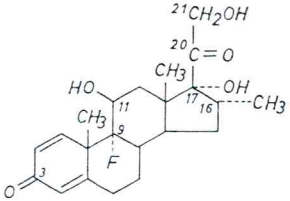
Cortisone
17α,21-Dihydroxy-4-pregnene-3,11,20-trione



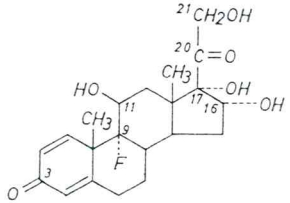
Prednisolone
11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione



Prednisone
17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione



Dexamethasone
9-Fluoro-11β,17,21-trihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione



Triamcinolone
9-Fluoro-11β,16α,17,21-tetrahydroxy-pregna-1,4-diene-3,20-dione

Indications for Glucocorticoids

In patients with normal adrenal function the pharmacodynamic activities of the glucocorticoids are utilized for various allergic and rheumatic diseases as well as other processes occurring in mesenchymal tissues. In all such cases therapy is only

symptomatic but can nevertheless often improve the condition decisively. This type of treatment is indicated for the following diseases: acute rheumatic fever and other rheumatic diseases, iritis, collagen diseases, acute attacks of gout, severe allergic reactions such as bronchial asthma (particularly status asthmaticus), agranulocytosis not resulting from toxic agents, as well as anaphylaxis and idiosyncratic reactions occurring during the course of infectious diseases, but only with simultaneous and sufficient antibacterial therapy. Further indications are nephrotic syndrome, lymphatic leukemia, hepatitis, and severe traumatic shock as well as long-term treatment of chronic obstructive bronchitis. Local application of steroids is frequently sufficient with dermatoses and infectious and allergic diseases of the eye. The same holds true with ulcerative colitis.

The administration of hydrocortisone in cases of adrenal insufficiency (Addison's disease) is true substitution therapy which should result in freedom from symptoms. Therapy with glucocorticoids can be attempted in cases of adrenogenital syndrome in order to inhibit the production of adrenal cortical hormones with androgenic activity.

Contraindications to Glucocorticoids

Prolonged treatment can be dangerous in the presence of hypertension, cardiac insufficiency, chronic nephritis, diabetes mellitus, myasthenia gravis, gastrointestinal ulcers, thromboembolic processes, bacterial infections without concomitant antibacterial therapy, and herpes corneae.

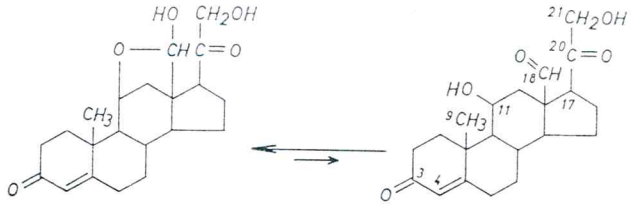
Dosage Schedule for Glucocorticoids

Since these compounds are orally active, this route of administration is generally chosen. Prednisone or prednisolone is recommended in daily oral doses beginning with 30 mg, and later 5–20 mg. The maintenance dose for a period of months is 5–8 mg per day. Since these compounds are metabolized rather rapidly in the body, the daily amount should be divided into three to four single doses. 6-Methylprednisone is given at a somewhat lower dose than prednisone. The dose of dexamethasone is six to seven times smaller than that of prednisone; triamcinolone requires a somewhat lower dose than prednisone. Intravenous administration is necessary in certain dangerous conditions. Hydrocortisone is infused at 10–12 mg/hr for 8 hr, or approximately 2.5 mg/hr of prednisolone sodium succinate. Suspensions of crystalline hydrocortisone or prednisolone are suitable for local injection. The same drugs with and without added antibacterial compounds are used in the form of ointments for the local treatment of skin disorders. The glucocorticoids can also be topically applied to the eye.

Mineralocorticoids

Aldosterone is the adrenal cortical hormone which under physiological conditions responds to changes in the volume and ion content of the extracellular space. Its

Aldosterone



Hemiacetal form

Aldehyde form
11β,21-Dihydroxy-3,20-dioxopregn-4-en-18-al

secretion is also dependent upon corticotropin under extreme conditions. The effect of angiotensin on aldosterone secretion has been mentioned on page 97. Aldosterone increases the reabsorption of sodium in the distal tubule of the kidney and simultaneously elevates the excretion of potassium. Water must be retained as a result of the sodium retention. A certain glucocorticoidlike activity on carbohydrate metabolism can be observed (oxygen at C-11?). On the other hand, the effects on mesenchymal tissue are completely absent.

Cortexone (11-deoxycorticosterone) had already been synthetically prepared before all other adrenal steroids were known. In general it acts like aldosterone. However, higher doses of cortexone are necessary for equally marked effects. Simultaneous administration of sodium chloride with large doses of cortexone causes hypertension and edema (potentially accompanied by necroses of the cardiac and skeletal musculature). This hypertensive effect has been used in animal experiments as a model for the testing of hypotensive drugs.

Mineralocorticoids alone are not sufficient for the treatment of adrenal insufficiency in man. However, mild cases of abnormal mineral metabolism can be normalized. The primary basis for therapy must always be glucocorticoids; mineralocorticoids may be added as a supplement. Since they are poorly absorbed from the gastrointestinal tract, they must be injected. Cortexone can also be given perlingually. The dose is generally 10–20 mg per day and later 2–5 mg per day. Since in experimental shock aldosterone improves the responsiveness of the vasculature to vasopressor drugs, the corresponding experiment might be justified in man as well.

The introduction of a hydroxyl group on carbon atom 11 is the last synthetic step that takes place in the adrenal cortex; this primarily results in the formation of hydrocortisone and aldosterone. This reaction is catalyzed by the enzyme, 11-β-hydroxylase. This enzyme can be selectively inhibited by certain drugs. Metyrapone is particularly active and prevents the formation of 11-hydroxysteroids in man. Principally it may be used in hyperaldosteronism. The resultant symptoms of deficiency occurring concomitantly must be balanced by the administration of

glucocorticoids. Such treatment has generally become superfluous in practical therapy owing to the introduction of aldosterone antagonists (cf. p. 104).

Gonads

Androgens

Male Sex Hormones

Testosterone is the testicular hormone produced by Leydig's interstitial cells. Its production is stimulated by the luteinizing hormone of the anterior lobe of the pituitary. Some compounds chemically related to testosterone (Δ^4-androsten-17β-ol-3-one) act more or less like testosterone. These compounds, together with testosterone, are classified as androgens. Testosterone is inactivated in the liver; when given by mouth it is ineffective.

Androsterone, which occurs in the urine, is a product of testosterone metabolism. It is a 17-ketosteroid with only weak androgenic activity. The remaining urinary 17-ketosteroids are derived both in the male and in the female from adrenocortical steroids.

Testosterone stimulates the development of the male secondary sexual characteristics. The symptoms of deficiency which occur after castration are completely abolished by sufficient substitution therapy. Psychic behavior is correspondingly altered. Testosterone can produce virilization in the female (hirsutism, enlargement of the clitoris, deep voice, acne vulgaris, etc.), which may be accompanied by changes in personality. An increase in libido has often been reported. These changes are dose dependent. In animal experiments, it has been possible to provoke aggressive or copulatory behavior by topical application of minute quantities of testosterone to certain areas of the brain.

Testosterone administration results in an increase in the mass of the skeletal musculature, which is accompanied by a positive balance in nitrogen, potassium, calcium, phosphate, sulfate, and chloride. The mechanism by which this increased protein deposition (anabolic effect) takes place is unknown. Androgens, like estrogens, stimulate the growth of an immature individual but then lead to a closure of the epiphyses so that the expected body height is more rapidly achieved but not exceeded. With elevated androgen levels, premature cessation of growth can also result because of premature closure of the epiphyses (i.e., adrenogenital syndrome).

The formation and secretion of hypophyseal gonadotropins is inhibited by large doses of testosterone and other androgens by a primary effect on the hypothalamus. In this way spermatogenesis is diminished. Atrophy of the testes can result. This effect is reversed upon withdrawal of the androgen. In cases of preexistent hypospermatogenesis, following termination of short-term testosterone administration, the decrease in spermatogenesis can be even more marked ("rebound" effect). Since the decrease in gonadotropin secretion is not specific as to sex, the corresponding effect can also be observed in females. Estrogen production is inhibited, ovula-

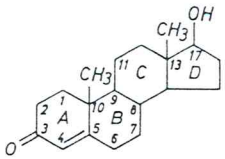
tion is suppressed, the menstrual cycle is interrupted, and the previously mentioned virilization occurs. In certain cases of mammary carcinoma, the androgens may have a favorable effect (cf. cytostatic agents, p. 301). Inhibition of hypophyseal secretion is presumed to be the mechanism primarily responsible.

The androgenic activity of a drug can be determined by the enlargement of the comb of a capon or the growth of the prostate and seminal vesicles in immature rats. As with all other biological assays, simultaneous comparison of the activity of the compound to be studied to that of a standard compound in the same animal species should always be carried out. Biological assay of chemically pure, known compounds is superfluous.

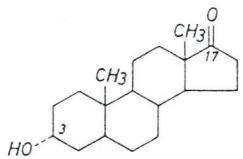
Derivatives of testosterone have been prepared in order (1) to prolong the duration of activity, (2) to make oral administration possible, and (3) to utilize the anabolic effect while diminishing the virilizing activity as much as possible.

The duration of action is prolonged by esterification of the C-17 hydroxyl group. Testosterone propionate is active for a few days; testosterone 17β-cypionate or testosterone enanthate are active for a few weeks. In these cases the absorption of the drug from the site of intramuscular injection is retarded.

Androgens with activity by the oral route can be achieved by methylation. This is true of methyltestosterone, for example, which nevertheless is administered perilingually or buccally for better absorption. Fluoxymesterone is effective by mouth and more potent than methyltestosterone. Mesterolone, in contrast to the other androgens, does not inhibit the release of gonadotropins; therefore testicular function is not diminished.

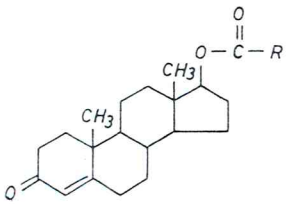


Testosterone
17β-Hydroxy-4-androsten-3-one



Androsterone, 3α-hydroxy-5α-androstan-17-one
Urinary excretion product

Depot preparation



Testosterone ester

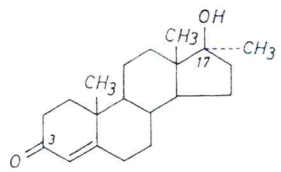
R = $-CH_2-CH_3$ Testosterone propionate

$-CH_2-CH_2-$ (cyclopentyl) Testosterone 17β-cypionate

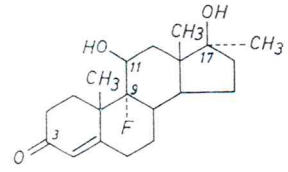
$-CH_2-CH_2-(CH_2)_3-CH_3$ Testosterone enanthate

Testosterone heptoate

Orally effective compounds



17-Methyltestosterone
17β-Hydroxy-17-methylandrost-4-en-3-one



Fluoxymesterone
9α-Fluoro-11β,17β-dihydroxy-17α-methyl-4-androsten-3-one

Indications

Substitution therapy is always successful in cases of androgen deficiency. With primary hypogonadism uninterrupted therapy with intramuscular injections of a testosterone ester with a long duration of action is indicated (i.e., testosterone enanthate, 0.25 gm every 3–4 weeks or testosterone caprinoylacetate, 0.3 gm 6–8 weeks apart). In many cases perilingual administration of 5 mg methyltestosterone two to eight times daily or 2–5 mg of fluoxymesterone daily by mouth produces a sufficient effect. In secondary hypogonadism and oligospermia, treatment should be interrupted from time to time with the hope of avoiding a rebound effect of the hypothalamic-hypophyseal system. When impotence is not the result of hormone deficiency, but of a psychic disturbance, the administration of androgen is ineffective. Increased libido in women has been observed following androgens; for example, after 5–10 mg methyltestosterone perilingually. Androgens sometimes inhibit the growth of mammary carcinomas for a certain period of time. Peripheral circulatory disorders may be influenced by androgens in a favorable manner. Complaints occurring during the first stage of prostatic hyperplasia are only subjectively improved.

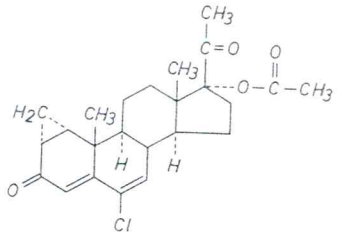
Side Effects

Frequently the most impressive side effects are symptoms resulting from the genuine hormonal action: virilization in the female, personality changes in children, functional disturbances of the anterior hypophysis which can produce an inhibition of the function and atrophy of the male and female reproductive glands. The growth of a preexistent prostate carcinoma can be stimulated by androgen administration. Sodium retention and the development of edema should be taken into account. Occasionally, cholestatic icterus results from the administration of high oral doses of androgens which are alkylated in the 17-carbon position. Such is the case for methyltestosterone, fluoxymesterone, and above all for the anabolic compounds.

Antiandrogens

An antiandrogen should be a specific antagonist of the androgens. On the basis of animal experiments, cyproterone appears to possess this property. Analogous

activity has been detected in man; for example, inhibition of libido, sebaceous gland secretions, and spermatogenesis. These effects appear to be completely reversible. Some success has been achieved with this drug in the treatment of criminal sexual behavior.



Cyproterone acetate
6-Chloro-17-hydroxy-1α,2α,methylene-pregna-4,6-diene-3,20-dione

Anabolic Compounds

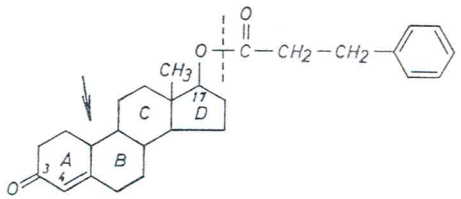
The relationship between the virilizing and the anabolic activities can be displaced in favor of the metabolic effects if the typical configuration of the A ring in testosterone (Δ^4-, 3-one, 10-methyl) is altered. These deviations have been marked with an arrow in the formulas for the anabolic drugs. The virilizing activity of these compounds is so markedly diminished that it only slightly appears with therapeutic doses or not at all. Nevertheless, following larger doses it cannot be avoided.

Indications

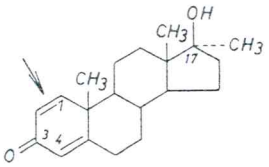
These compounds are indicated in relative or absolute protein deficiency only if diet alone does not produce the desired results. It should always be kept in mind that the anabolic effect can only be expected to occur during the period over which these

Anabolic angents

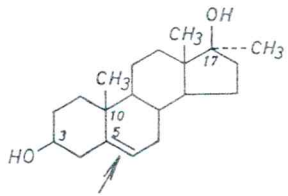
(Arrows indicate the differences from the androgens)



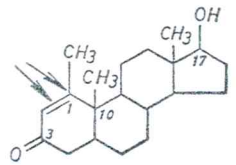
Nandrolone phenpropionate
19-Nor-17β-hydroxy-3-ketoandrostene 17-phenylpropionate



Methandrostenolone
17β-Hydroxy-17α-methylandrosta-1,4-dien-3-one



Methandriol
17α-Methyl-5-androstene-3β,17β-diol



Methenolone
17β-Hydroxy-1β-methyl-5α-androst-1-en-3-one

drugs are being given. Individual indications for their use are anorexia nervosa, iatrogenic hypercorticism, cachectic conditions in cases of chronic infection or tumors, osteoporosis, radiation sickness, and with poorly healing bone fractures. Anabolic compounds are used without any medical indication by athletes in order to increase the amount of muscle tissue.

Side Effects

These correspond to those of the other 17-alkylated androgens. A deepening of the voice can occur in women which under certain circumstances is irreversible. Cholestatic hepatitis and changes in liver function have been observed. Prolonged administration in children is associated with retardation of bone growth and premature closure of the epiphyses. Anabolic drugs are contraindicated in prostatic carcinoma, and during pregnancy because of the possible virilization of the fetus.

Female Sex Hormones

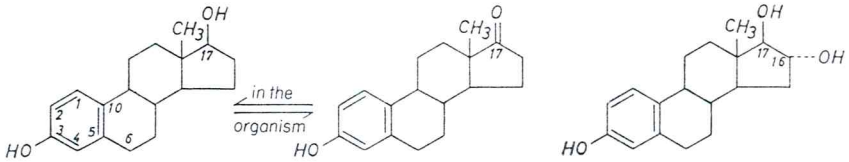
Two chemically related but different acting compounds, estradiol and progesterone, are produced by the ovaries under the influence of hypophyseal gonadotropins. Estradiol is probably produced in the theca interna cells of the ovary under the influence of interstitial cell stimulating (luteinizing) hormone. Under the influence of luteinizing hormone, progesterone is released from the corpus luteum or formed in the placenta. Estradiol and compounds with similar pharmacological activity are called estrogens; progesterone and compounds of corresponding activity are called progestins.

Estrogens

Estradiol affects the bodily development and the psychological behavior typical of the female sex. The growth of the uterine musculature is stimulated. The endometrium reaches the state of development characteristic of the proliferation phase of the estrous cycle. Simultaneously, characteristic alterations in the mucosa of the cervix and the vaginal epithelium take place. The development of milk ducts in the breast is promoted. If the administration of estradiol is abruptly interrupted after 2 weeks of therapy in an amenorrhoeic, nonpregnant woman, "withdrawal" bleeding sets in, with discharge of the proliferated uterine mucosa. Continued

administration of high doses of estrogens produces a glandular-cystic hyperplasia of the endometrium. Estrogens in high doses inhibit the secretion of hypophyseal gonadotropins via a hypothalamic mechanism (cf. also the effects of the antiestrogen, clomiphen, p. 242). Consequently, the ovaries will atrophy; the formation of follicles and ovulation are suppressed. This process is reversible as long as the treatment has not lasted too long. Estradiol implants in the ventromedial, premammillary hypothalamus of the rabbit induce sexual activity despite inhibition of ovarian function. The steroid has a direct, central effect; corresponding results have been obtained with androgens (cf. p. 235).

The keratinization of vaginal epithelial cells induced by estradiol and other estrogens in castrated or immature female rats and mice can be used as the basis for the biological assay of estrogens.

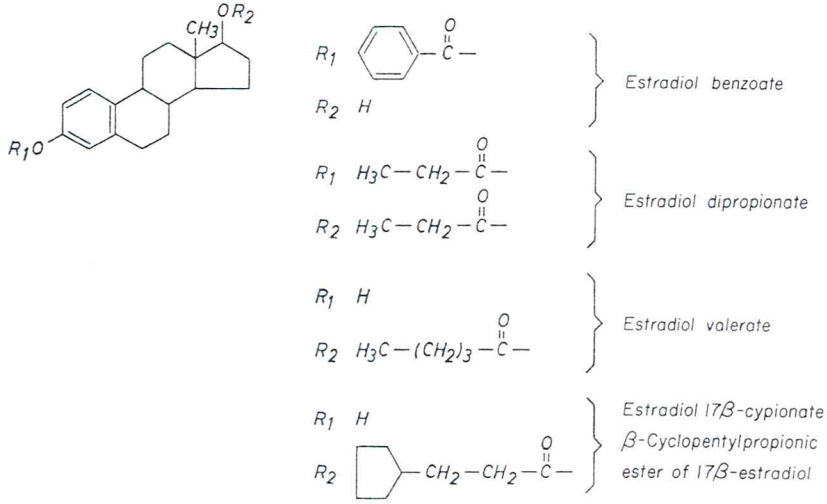


β-Estradiol
estra-1,3,5(10)-triene-
3,17β-diol

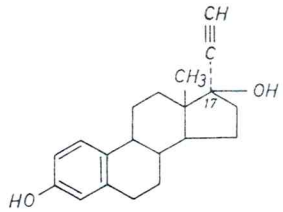
Estrone
3-Hydroxyestra-1,3,5(10)-
triene-17-one

Estriol
Estra-1,3,5(10)-triene-3,
16α,17β-triol

Depot preparations



Orally active preparation



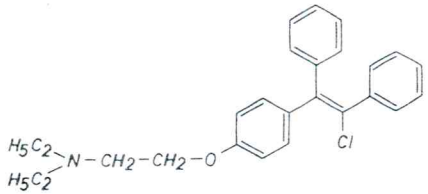
Ethynylestradiol
17α-Ethinylestradiol,
the 3-Methylether is mestranol

Estradiol is primarily inactivated in the liver. For this reason it hardly shows any activity when given by mouth. Metabolites, principally estrone and estriol, are excreted in the urine. Under certain circumstances larger amounts of estradiol are found in the urine of patients with liver damage than in that of normal subjects. Some of the estrogens appear in the urine after conjugation with glucuronic or sulfuric acid. Estrone and estriol have only slight estrogenic activity. Estriol has no activity on the endometrium but does exert an estradiollike effect on the cervix and vaginal mucosa, possibly because these tissues respond to less potent estrogens.

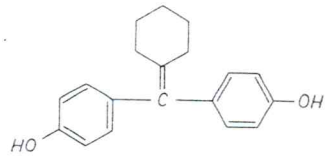
A large number of steroids with estrogenic activity has been produced in order to (1) extend the duration of action of estradiol, which is short, and (2) obtain orally active compounds. Upon intramuscular injection, various estradiol esters, for example, estradiol benzoate and estradiol dipropionate, have a duration of action of several days as the result of slower absorption and most likely a diminished rate of metabolism. The effects of estradiol valerate and estradiol cyclopentylpropionate last for about 3 weeks. Qualitatively, all these compounds have the same effects. Ethinylestradiol is particularly resistant to inactivation in the gastrointestinal tract and the liver. Therefore, it is active by mouth even in very small doses. A mixture of estrogen sulfates obtained from horse urine also has a mild estrogenic effect following oral administration.

Stilbene Derivatives

With Estrogenic Activity. For some time compounds with estrogenic activity have been known which are not steroids but which have the basic structure of stilbene or other closely related compounds. Diethylstilbestrol (formula, cf. p. 227) exhibits in every respect the same estrogenic effects as estradiol. Quantitatively, its potency is of the same order of magnitude as that of estradiol but the loss of activity following oral doses is small. Because of its short duration of action, this compound was earlier implanted as a pellet. At present, analogous with the estradiol esters, derivatives with a longer duration of action are generally preferred. Examples are diethylstilbestrol dipropionate or diethylstilbestrol dimethylether. Compounds lacking the double bond between the two central carbon atoms (hexestrol) or with three carbons between the phenyl rings (benzestrol) are also active.



Clomiphene
2-[p-(2-Chloro-1,2-diphenylvinyl)phenoxy]-triethylamine



Bis(p-hydroxyphenyl) cyclohexylidenemethane

WITH ANTIESTROGENIC ACTIVITY. Clomiphene is chemically related to the estrogenic stilbene derivatives and shows antiestrogenic activity in animal experiments. However, this "peripheral" effect is overshadowed in man by an excitation of the hypothalamic-anterior pituitary system which results in an increased secretion of gonadotropin. It probably involves a release from the preexistent inhibitory effect of the natural estrogens. Therefore, this effect may also be explicable on the basis of the antiestrogenic property of clomiphene. This compound has already been successfully utilized to stimulate ovulation in some cases of sterility.

WITH ANTIPROGESTIN ACTIVITY. By shortening the distance between the two aromatic rings of stilbene to one carbon atom, compounds are obtained having weak estrogenlike activity, but possessing marked antiprogestin effects. Such a compound is bis(*p*-hydroxyphenyl) cyclohexylidenemethane. It inhibits the activity of progesterone, but particularly the synthesis of progesterone in the ovary. For this reason it is active as an abortifacient in experimental animals.

Side Effects of Estrogens

The side effects that are directly dependent on the estrogenic activity of these compounds, such as hyperplasia of the endometrium and inhibition of ovarian function, have already been discussed. The earlier assumption that abortions could be produced by large doses has not been confirmed. Nevertheless, the administration of estrogens during early pregnancy has led to decidual necroses and disturbances in nidation. In most cases estrogens seem to prevent pregnancy when given on the day after insemination and on the following 4–5 days in high doses, a "morning after pill." Estrogens can result in sodium retention and eventually edema formation. These phenomena can be balanced by a low sodium diet or by saluretics. If large doses of stilbene derivatives are too rapidly absorbed, the result is nausea, vomiting, mild diarrhea, and headache. These side effects are less pronounced with the stilbene derivatives possessing a more prolonged action. Dermatological changes may occur. (Concerning the danger of the development of thromboembolic diseases see section on oral contraceptives.)

Indications and Use of Estrogens

Estrogens are administered for substitution therapy in all cases of ovarian insufficiency. They must be given at the proper point in the menstrual cycle, about the 8–19th day in order to avoid disturbances of the cycle. Postmenopausal complaints, senile vaginitis, kraurosis vulvae, and pruritus vulvae are also often successfully treated. Twenty-five to 30 mg of estradiol benzoate given over a period of 12–14 days is sufficient to elicit the proliferation stage in a castrated woman. If 200–250 mg of a depot preparation of progesterone is subsequently injected, menstruallike bleeding results after a further 10–14 days. Depending upon the indications, a depot preparation of estradiol can be used in place of the short-acting estradiol benzoate.

Oral therapy in mild cases, for example climacteric complaints, is accomplished with a conjugated estrogen, otherwise preferably with ethinyl-estradiol which requires a 10–20-fold lower dose than does estradiol. In an analogous way diethylstilbestrol dipropionate can be given by mouth but in similar doses to those of estradiol benzoate. Estrogens in very high doses, possibly in combination with castration, often have a favorable effect in prostatic carcinoma and its metastases. The growth of the carcinoma is markedly inhibited for months or even years. Such therapy must be continued without interruption. Even if all symptoms have disappeared, a cure is not possible. The doses for this type of therapy are 3–5 mg tablets of diethylstilbestrol dipropionate daily by mouth; later 1.5–3 mg and possibly corresponding doses by intramuscular injection. Unfortunately, it has been shown that a lethal outcome due to thromboembolic disease is considerably increased as a result of therapy with estrogens. For this reason the advantages and disadvantages of such treatment should be carefully considered. Estrogens, sometimes administered in order to stop lactation, also increase the danger of thromboembolic episodes after delivery. Estrogens should not be used for this purpose. Estrogens are also occasionally active in cases of mammary carcinoma.

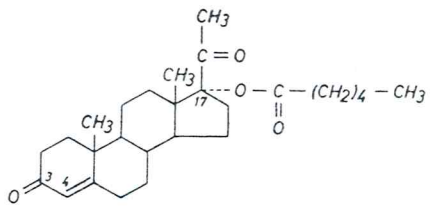
Progestins

Progesterone elicits the secretion phase in the endometrium only after the proliferation phase has been initiated by estrogen. Simultaneously, the resting temperature of the woman is somewhat elevated. If there is a sudden fall in the progesterone level in the blood at the end of the normal cycle or with cycle-imitating therapy with estrogen and progesterone, withdrawal bleeding results. In the milk glands progesterone promotes the development of the alveoli. Moreover, it is necessary for the implantation of the ovum. The progesterone required for the maintenance of pregnancy originates from the corpus luteum only during the first 2 months of pregnancy; later it is produced by the placenta. Progesterone in high doses, just as with androgens and estrogens, reduces gonadotropin secretion. Thereby, it inhibits the development and function of the gonads. The inhibition of ovulation and the estrous cycle is of practical importance. There develops a condition corresponding to pregnancy but without the presence of a fetus.

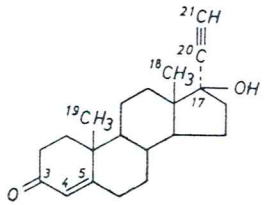
As might be inferred from the chemical structure, progesterone has weak andro-

genic activity which, in contrast to the nortestosterone derivatives, is not expressed as a masculinization of the fetus. On the other hand, the androgens also have certain progestinal effects. Both groups of compounds have a weak antagonistic effect with regard to estrogens. The standardization of progesterone activity is performed by observing the endometrium of immature rabbits that have been treated with progesterone following pretreatment with an estrogen.

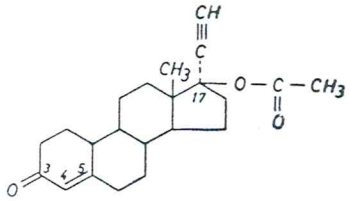
Progestins



17α-Hydroxyprogesterone caproate
Progesterone formula on p. 228



Ethisterone
17α-Ethynyl-17β-hydroxy-4-androsten-3-one



Norethindrone acetate
17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one

Progesterone is largely inactivated after ingestion by mouth. On the other hand, it is active by perilingual administration. Intramuscular injection is the preferred route of administration. The principal metabolite is pregnanediol, which is formed particularly in the liver and excreted as a glucuronide in the urine.

Analogously to the androgens and estrogens, esterification with long-chain fatty acids at C-17 produces a considerable prolongation of activity and an increase in potency; such a compound is hydroxyprogesterone caproate. This compound, with a duration of action of 1 week or longer, depending upon dose and conditions, resists the normal mechanism for the degradation of progesterone; pregnanediol excretion in the urine does not increase. As with progesterone and in contrast to the oral progestins derived from nortestosterone, this drug does not induce virilization of the fetus.

As with estradiol, the introduction of an ethynyl group into testosterone also results in good oral activity. The androgenic properties are largely lost and the

progestin ethisterone is obtained. The ethynyl group replaces C-20 and C-21 (the keto oxygen at C-20 of progesterone is replaced by a triple bond). This is a further example that the electron configurations of a carbonyl oxygen atom and double or triple bonds correspond approximately and have similar biological effects. Closely related and active in analogous fashion is the corresponding derivative of 19-nortestosterone, norethisterone. Other compounds with qualitatively the same activity have been prepared; generally they differ only in the placement and number of double bonds in the A ring of the steroid nucleus.

Side effects of progestins can be used for a therapeutic effect in disturbances in the menstrual cycle, delay of menstruation, and suppression of ovulation. With the use of normal doses and proper administration with regard to the cycle, side effects are rare. With longer term administration of progestins for suppression of ovulation and menstruation, one must expect disturbances in general well-being in about 25% of all cases. Pain from distention in the breast, headaches, nausea, vomiting, and diarrhea occur. In addition the libido is diminished and sodium and water retention can take place, resulting in an increase in body weight. In less than 10% of the cases utilizing the usual doses for the suppression of ovulation and in those preparations containing estrogens, endometrial bleeding occurs. In susceptible individuals following large doses, an aggravation of bronchial asthma, epilepsy or migraine along with reversible impairment of liver function can be expected. The danger of masculinization of the female fetus (nonadrenal pseudohermaphroditism) exists with the use of oral progestins during pregnancy between the eighth and thirteenth week. Also in women, the intake of ethynyltestosterone preparations can produce symptoms of virilization. Progesterone and hydroxyprogesterone caproate do not lead to masculinization. Progestins are contraindicated in adolescents with an unstable cycle, in all cases in which a tendency toward thrombosis exists, and in cases of recent icterus.

Indications

In glandular-cystic hyperplasia, a progesterone depot preparation in a dose of 200–250 mg together with a small dose of estrogen is injected intramuscularly. To build up the secretion phase in primary and secondary amenorrhea, daily 5 mg doses of progesterone intramuscularly or a corresponding depot preparation after pretreatment with an estrogen is given from the fifteenth day onward. The efficacy of progestins in cases of habitual and threatening abortion is controversial, even when evidence for an insufficiency of the corpus luteum is present, i.e., if the preganediol secretion in the urine is diminished. For such an indication very high doses are used; i.e., hydroxyprogesterone caproate 250–500 mg intramuscularly every week. Oral progestins for a more long lasting suppression of ovulation are called for in endometriosis and possibly to avoid the loss of blood during therapy with anticoagulants.

Oral Contraceptives

Prevention of conception is possible by suppression of ovulation by inhibiting hypothalamic centers through administration of progestins or estrogens. Addi-

tionally, local conditions are also of importance. Progestins change the quality of the cervical secretions and diminish the tendency toward implantation in the endometrium. Under certain circumstances either of these last two factors is sufficient for contraception. Thus the administration of a progestin alone can prevent conception, although ovulation still occurs. On the other hand, the sole use of estrogens is not practiced because of the side effects. The usual contraceptive therapy consists of simultaneous administration of both female sex hormones (one-phase treatment) and it is restricted approximately to the 5th to 24th day of the cycle. Several days following discontinuation of progestin administration bleeding occurs. Spontaneously, cycles occur again and pregnancy is possible. After prolonged use of oral contraceptives, ovulation may not occur for as long as 3 months after the treatment is stopped. In sequential therapy (two-phase treatment) ovulation is suppressed by an estrogen and a progestin administered toward the end of the cycle. Generally, the classical "one-phase" treatment is preferred, since it is more reliable. The risk of an undesired pregnancy is rather low, provided that the preparations are properly used; approximately one pregnancy occurs in 1200 cycles. The interval between two doses must not exceed 36 hr, since the desired effect of the hormones does not persist for a longer period of time. Exceeding this interval renders the action of the contraceptive uncertain, even if it is taken regularly over the remaining period of the current cycle. Similarly, the effect is not certain during the first cycle after beginning treatment or after a new start following interruption. Attempts to prevent contraception for either 1 or 3 months with a single injection are not sufficiently reliable or are unfavorable because of the risk of overdosing.

Overall judgment after 15 years of experience indicates that important damage to health does not occur. Statistical analysis of large numbers, however, suggests that at least for one disease the risk is increased—thromboembolic disorders. This risk is brought about by the estrogen component. It is dose dependent, as shown by the following: 0.05 mg estrogen daily = relative risk 1; 0.075 mg = 1.2; 0.1 mg = 1.6; 0.15 mg = 2.4. For this reason only preparations should be given that do not contain over 0.05 mg of estrogen (ethinylestradiol or mestranol) as a daily dose. It should be realized, however, that pregnancy in itself carries a much greater risk. The increase of coagulation factors in blood and an enhanced aggregation of the thrombocytes contribute to the increased clotting tendency of the blood. In healthy women these changes induced by contraceptives remain within the normal range. However, they may gain importance in circumstances of primary pathology (e.g., cerebral thrombosis in young women with a tendency to fainting) or under additional stress (e.g., surgical interventions). A certain impairment of liver function and an increase in blood pressure may be diagnosed occasionally. In extremely rare cases the occurrence of cholestatic hepatoses, vaginitis caused by *Candida albicans*, chloasma, and inflammation of the gingiva have been reported.

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CHAPTER 6

VITAMINS

Vitamins are compounds necessary for the normal function of the organism which must be obtained from exogenous sources (including synthesis by intestinal bacteria). There is only a single indication for the use of vitamins: substitution therapy in cases of deficiency. A true vitamin deficiency seldom occurs with the average European or American diet. Vitamin A and particularly vitamin D should be given prophylactically in early childhood and during pregnancy and periods of lactation. A deficiency not dependent on diet may occur with vitamin B_{12} and vitamin K. This has been treated in detail in the sections on anemia and blood clotting. With atrophy of the gastric mucosa, B_{12} deficiency (loss of intrinsic factor) occurs and lack of vitamin K is secondary to antibiotic therapy (sterilization of the intestine) or a relative deficiency with overdosage of coumarin derivatives. For individuals in vitamin balance, the additional administration of vitamins (polyvitamin preparations) results in no "tonic" or infection-preventing activity nor does it have pharmacological activity or any type of gerontological effect.

Vitamin A

Vitamin A is the precursor of visual purple. In addition, epithelial cells require this vitamin for normal growth and function. Correspondingly, deficiency leads to visual disturbances (beginning with night blindness) and to epithelial damage (xerophthalmia, keratomalacia). Daily oral doses of vitamin A between 25,000 and 50,000 IU are sufficient for substitution therapy. Vitamin A occurs in green leafy vegetables, partly in the form of the provitamin carotene, and in higher concentrations together with vitamin D in cod liver oil.

Toxic symptoms occur following long-term administration with very large doses (overzealous parents). These are anorexia, irritability, and dry skin with bleeding at the corners of the mouth. Characteristic signs of poisoning are periosteal swelling and deposition that are painful and limit movement. The liver is sometimes enlarged and with infants the fontanel protrudes as a result of an increase in intracranial pressure. Fetal malformations have occurred following considerable overdoses of vitamin A during pregnancy. The oxidized form of vitamin A, i.e., vitamin A acid (retinoic acid) enhances growth only, without influencing visual function. In a considerable number of cases basal cell carcinoma may be cured upon prolonged topical application.

Vitamin B Complex

Vitamin B_1 (thiamine, aneurin) in the phosphorylated form is the coenzyme of carboxylase. Correspondingly, thiamine deficiency leads to insufficient degradation of α-keto acids. This is especially noticeable when carbohydrates form the primary source of energy. A corresponding condition also exists if ethyl alcohol is the most important energy source in the diet ("chronic alcoholism"). The disease beriberi is characterized particularly by damage to peripheral nerves with corresponding disturbance of the muscular innervation and signs of myocardial insufficiency with arrhythmias. The daily requirement for thiamine is about 1–2 mg; this need is considerably elevated with a pure carbohydrate diet. In cases of vitamin B_1 deficiency (beriberi) 5 mg are administered several times daily by mouth. A therapeutic effect has not been demonstrated in neuritis of other origins, even with high doses (100 mg intravenously). On the contrary, parenteral administration can result in lethal anaphylactic shock. There appears to be a greater requirement for thiamine during pregnancy. Possibly, neuritis in pregnant women can be successfully treated with thiamine. The enteral absorption of fat-soluble derivatives of thiamine such as diacetylthiamine and thiamine tetrahydrofurfuryl disulfide is better than that of thiamine itself.

Vitamin B_2 (riboflavin) in the phosphorylated form is also a component of a coenzyme. Symptoms of deficiency appear as lesions at the corners of the mouth, cheilitis, stomatitis, and a characteristic corneal vascularization. The daily requirement is about 3 mg. Toxic symptoms resulting from an overdosage are not known.

Nicotinamide (3-pyridinecarboxylic acid amide) is a component of a large number of enzymes. Lesions of the skin and mucous membrane occur with slight deficiencies; in extreme cases the picture of pellagra occurs. The daily requirement is estimated to be 10–20 mg. A dose of 100–200 mg per day is given for the treatment of deficiency disease. Nicotinic acid (niacin) is also effective. The latter has in addition to its vitamin activity a pharmacological effect of cutaneous vasodilatation. This activity of nicotinic acid and its esters is utilized in rheumatoid rubbing ointments in order to increase the local blood flow.

High doses of nicotinic acid depress an elevated cholesterol level in many patients. The mechanism of action is unknown; a therapeutic effect in arteriosclerosis seems not to have been demonstrated. Since in addition hepatic damage can occur, such therapy is not recommended.

Vitamin B_6 (pyridoxine) is, again in phosphorylated form, the coenzyme of amino acid decarboxylases and transaminases. Vitamin B_6 deficiency in man has only been demonstrated under experimental conditions. The daily requirement is estimated to be about 2 mg. High doses of pyridoxine (100–300 mg) are supposed to have a favorable effect in radiation damage, vomiting during pregnacy, and peripheral nerve damage caused by isoniazid administration.

Vitamin C (Ascorbic Acid)

Vitamin C forms a redox system which is involved in many aspects of cellular metabolism. The pathophysiological mechanism of vitamin C deficiency disease is known only in part. For example, vitamin C is necessary for proline hydroxylation, an important step in collagen formation. A deficit in ascorbic acid leads to scurvy and hemorrhagic diathesis. Accordingly, these diseases are cured by the administration of vitamin C. In the absence of fresh vegetables and fruit, vitamin C can be given prophylactically (20–50 mg daily). The often-recommended intake of very high doses (1 gm) for protection against colds or the promotion of defense against infection is not well founded. An overdosage with ascorbic acid is not dangerous; excess vitamin C is rapidly excreted by the kidney.

Vitamin D

Several fat-soluble vitamins which occur in fish liver and plants are collectively known by the term vitamin D. Vitamin D is also formed in human skin exposed to sunlight. Ultraviolet irradiation of ergosterol *in vitro* results in formation of vitamin D_2 (calciferol). Irradiation of 7-dehydrocholesterol yields vitamin D_3 (cholecalciferol). Forty thousand IU of vitamin D_3 corresponds to 1 mg of the crystalline compound.

The absorption of calcium and phosphate from the intestine takes place under the influence of vitamin D. Lack of the vitamin impairs this process so that insufficient material is available for the formation of bone. In the body vitamin D_3 is converted to 25-OH-cholecalciferol, the actual active compound. It enhances the formation of a specific protein in the intestinal mucosa that is responsible for the absorption of calcium from the intestinal lumen. On the other hand, vitamin D also contributes to the maintenance of a constant blood calcium level by mobilizing calcium from the bones.

Vitamin D also has an effect upon phosphate excretion by the kidney and thus contributes to the maintenance of a constant level of plasma phosphate. Finally,

the vitamin specifically elevates the citrate concentration in blood, bone, and urine. Possibly, this activity is related to the mobilization and transport of calcium from the bone into the blood. As a result of these effects, the calcium level, and thereby also the concentration of ionized calcium in the blood, is elevated by vitamin D.

Toxicity and death have resulted from vitamin D overdosage. With long-term treatment the daily dose should not exceed 5000 IU per kg (0.125 mg/kg). The symptoms (calcinosis) are the expression of the considerable increase in the blood calcium level. The excretion of calcium and phosphate in the urine is elevated. The calcium mobilized from the bones is deposited in soft tissues, particularly the kidney and in the media of blood vessels. Clinical symptoms are loss of appetite, disturbances in the gastrointestinal tract, headache and joint pain, muscle weakness; in children, tremor, twitching, and arterial hypertension. Death usually results from the inhibition of renal function. These effects are reversible upon prompt cessation of vitamin D administration. Even the calcium deposits disappear, leaving only slight, scarlike traces.

Indications

For the prophylaxis of rickets during infancy 0.025 mg (1000 IU) of a vitamin D preparation is given daily by mouth. For small children about 0.05 mg of a vitamin D preparation is given daily during the first year, beginning at the end of the first week of life and also during the winter of the second year of life. For the therapy of rickets itself, about 0.25 mg (10,000 IU) is given daily. One-shot prophylaxis is achieved by the oral administration of 10 mg with one or two repetitions in intervals of 3 months; for rickets therapy 15 mg is given. Since the extent of absorption is uncertain with single high doses, "one-shot" therapy and prophylaxis entail a risk. Severe damage and death have occurred from idiopathic hypercalcemia. Intramuscular injections are necessary in premature infants and in cases of faulty absorption.

Dihydrotachysterol

The ultraviolet irradiation of ergosterol results in compounds, along with vitamin D_2, in which the vitamin activity is much weaker, but in which the "calcinotic" activity still remains. By hydrogenating one of these compounds, tachysterol, dihydrotachysterol is obtained which chemically is hardly different from vitamin D_2. At C-10 it contains a methyl group instead of the methylene group of vitamin D_2. This compound has only about 1/500 times the antirachitic activity of the vitamin but in suitable doses is able to elevate the concentration of calcium, including the ionized portion, in the serum. It is therefore used successfully to normalize the serum calcium level in cases of hypocalcemic, tetanic conditions (e.g., hypofunction of the parathyroid). In practice, complete substitution therapy is possible in the absence of parathyroid glands. Its advantage lies in the possibility of oral administration and long-term activity. If necessary, such therapy must be continued throughout the course of life.

It is nevertheless questionable whether it is necessary to use this relatively expensive drug since the same activity can be obtained with high doses of vitamin D_3. The danger of toxicity is similar with both dihydrotachysterol and vitamin D_3 since with overdoses in both cases the danger of hypercalcemia and calcium deposition in the blood vessels and kidneys exists. The serum calcium levels should be monitored regularly in every case of treatment of hypocalcemia. It should not rise above normal levels. The initial dose of dihydrotachysterol with manifest tetany is 8–15 mg by mouth. The maintenance dose is 1–7 mg per week depending upon the serum calcium levels.

CHAPTER 7

THE THERAPY OF INFECTIOUS DISEASE

Disinfectants and Antiseptics

Compounds in this group must fulfill quite different requirements, depending on whether they are to be used on humans, or on inanimate objects (instruments, waste disposal, drinking water, etc.). An ideal disinfectant or antiseptic for human use should possess the following properties. (1) It should have a potent bactericidal (disinfectant) action or a bacteriostatic (antiseptic) effect. (2) Human skin, mucous membrane, and injured tissues must tolerate the agent well. (3) If ultimately absorbed, it should have little or no systemic toxicity. In this context it should be reemphasized that the most potent antiseptic is not necessarily the best agent, but rather that here again the therapeutic index must be considered. The best agent is that which exhibits the most marked difference in the concentration damaging to bacteria and the concentration which elicits toxic symptoms. (4) The compound should also be active against all types of bacteria and their spores and thus lack the specificity expected of chemotherapeutic agents and antibiotics. (5) As far as possible, its activity should not be diminished by the presence of "inactivators" (pus, blood, hydrogen, or hydroxyl ions). (6) Its physical and chemical properties should be suitable (stability, solubility, rapidity of onset of its action, etc.).

Disinfectants (the term is used in the following discussion to include antiseptics) belong to a wide variety of chemical classes. A classification of these agents, although somewhat arbitrary, is best achieved on the basis of their chemistry.

1. Phenols
2. Alcohols, aldehydes, acids

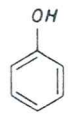
3. Oxidizing agents
4. Halogens
5. Surface-active agents
6. Heavy metal salts
7. Acridine and quinoline derivatives
8. Furan derivatives

Phenol Derivatives

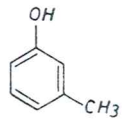
Phenol

Phenol (carbolic acid) is a poor disinfectant and is only of historical interest. In order to kill bacteria, concentrations in the range of 0.2–1% are necessary. These denature the bacterial protein without causing coagulation. Phenol penetrates membranes very readily and is therefore easily absorbed following surface application. In concentrations of 1% and higher it precipitates protein and therefore destroys tissues. Since it acts simultaneously as a local anesthetic, tissue necrosis may occur without pain.

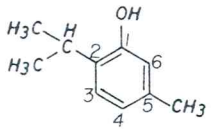
In cases of toxicity resulting from absorption, the symptoms are dependent upon the amount of phenol taken up. Following the uptake of large doses, the symptoms of central nervous system toxicity predominate including convulsions, loss of



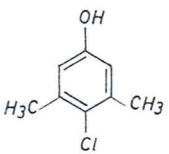
Phenol



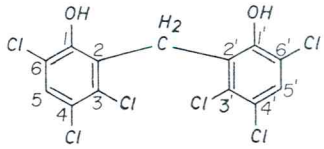
m-Cresol



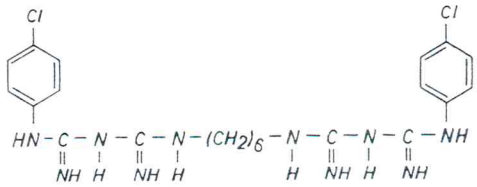
Thymol
5-Methyl-2-isopropyl-1-phenol



4-Chloro-3,5-xylenol



Hexachlorophene
2,2'-Methylenebis[3,4,6-trichlorophenol]



Chlorhexidine
1,1'-Hexamethylenebis[5-(p-chlorophenylbiguanide)]

consciousness, and death resulting from respiratory paralysis. If this acute toxicity is withstood or the amount of phenol taken up is smaller, the kidney as the excretory organ for phenol and its metabolic products shows the most severe toxic symptoms: albuminuria, hematuria; and the urine is darkly colored by the oxidation products of phenol. Therapy of such intoxication is symptomatic. Phenol can be converted by chemical substitution into agents which possess a more potent bacteriocidal activity and a larger therapeutic index. The potency increases with the number of substituted chlorine atoms. The same holds true for the introduction of alkyl residues (cf. cresol and thymol). The combination of both substituents further accentuates the degree of effectiveness.

Cresol

The methylphenols are about three times as active as phenol while possessing the same toxicity. Crude cresol consists of at least 50% *m*-cresol. The other two isomers are essentially as effective. The yellowish-brown, oily liquid which is poorly water soluble can be utilized for disinfection of rooms, etc.

In order to improve the water solubility and the wetting ability, cresol is commonly used in combination with soaps (seponated cresol solution N.F.). Such preparations contain 50% cresol. In concentrations corresponding to a 1% cresol solution, this preparation is suitable for disinfection of the hands, in 5% concentration for disinfection of instruments. These simple cresols have largely been replaced by more effective agents.

Thymol

Isopropylcresol is about 30 times as active as phenol and possesses less absolute toxicity. The water solubility of thymol is poor; however the achieved concentration is sufficient for the bacteriostatic effect (approximately 3×10^{-4} gm/ml). It is used as a preservative in clinical laboratories, and solutions of 5% in alcohol are used for disinfection of the skin. Particularly noticeable is the potent fungicidal activity of thymol which finds use in the therapy of fungus diseases of the skin.

Chlorinated Phenols

The compounds 4-chlorocresol and 4-chloroxylenol are good disinfectants. Commercial preparations contain combinations of the two agents. Concentrations of 0.5–5% in soap solution are used for the disinfection of the skin and mucous membranes, as well as instruments and rubber gloves. 4-Chlorothymol is also more potent than thymol; compared to phenol it is about 75 times as potent as a bacteriocidal agent while its toxicity is low. A 5% solution in dilute alcohol is suitable for disinfection of the hands.

Hexachlorophene is a compound that is practically water insoluble; its disinfectant activity exceeds that of phenol by about a factor of 100. Toxicity is low and local irritant effects are very slight. The compound is added to solid or liquid soaps in concentrations of about 2–3%. With daily use the number of gram-positive skin bacteria is considerably diminished. However, it is not possible with this procedure to acutely disinfect the hands. Hexachlorophene is a constituent of

deodorant soaps since it impairs the bacterial decomposition of sweat and thereby the production of unpleasant-smelling compounds.

Chlorohexidine is likewise suitable for disinfection; in particular there has been good experience in its use for the treatment and prophylaxis of infections of the bladder with otherwise resistant bacteria. Infections following upon catheterization can be largely avoided if at the conclusion of this procedure chlorohexidine (50 ml, 0.02%) is instilled into the empty bladder. A 0.1% solution of this compound in oil is suitable for the disinfection of instruments and apparatus.

Polyvalent Phenols

Resorcinol and its derivatives, hexylresorcinol and pyrogallol, indeed have disinfectant properties but are not used for this purpose since their activity is too low.

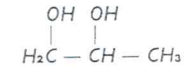
Alcohols, Aldehydes, Acids

Alcohols

Primary alcohols have a bacteriocidal activity that increases with increasing molecular weight. For medicinal purposes only ethyl alcohol and the propyl alcohols are of importance. For surgical disinfection of the hands, approximately 80% ethanol and 70% *n*-propanol must be used (the earlier value of 35% for the propyl alcohol is not sufficient). Bacterial spores are not destroyed by these concentrations. Alcohols alone are not sufficient for the disinfection of instruments. Since the alcohols rapidly evaporate, their activity is very transient.

Glycols

A series of polyvalent alcohols can be used under certain circumstances for the disinfection of air spaces. For example, propylene glycol and triethylene glycol are potent bacteriocidal and fungicidal agents in the vapor form. The required vapor concentrations are approximately 0.5 mg propylene glycol or 0.005 mg triethylene glycol per liter of air. This marked effect is even more astonishing since these glycols are practically nontoxic for microorganisms in the form of solutions.



Propylene glycol
1,2-Propanediol

Triethylene glycol

In order that the disinfectant activity in the air can occur, the following conditions must be fulfilled: the air must contain a certain quantity of water; the water content must be sufficient for all bacteria to be contained in microdroplets of water. The glycol rapidly dissolves in these microdroplets and achieves a high concentration which is bacteriocidal. Since with increasing humidity the amount of glycol which can be vaporized into the atmosphere diminishes, there exists an optimal humidity

for disinfecting air spaces. The glycols are not active at the extreme values (absolute dryness and water-saturated air). The toxicity of these glycols is relatively low for mammals.

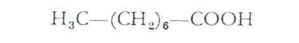
Aldehydes

Among the aldehydes, only the simplest compound, formaldehyde, is of importance for disinfection. Because of its strong irritant effect, it is not suitable for use on living tissue but only for the disinfection of rooms and the sterilization of sputum, etc. Besides bacteria, it also kills viruses.

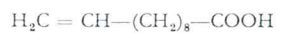
Dilute solutions of formaldehyde have an astringent effect and inhibit the secretion of sweat. In place of formaldehyde, hexamethylenetetramine in the form of paste or a solution can be used; formaldehyde is liberated from this compound by the acidic sweat. Occasionally, orally administered hexamethylenetetramine (methenamine) is still used as a disinfectant for the urinary tract. The formaldehyde does not reach the renal parenchyma. Simultaneous acidification of the urine (i.e., with ammonium chloride) should be assured, since the liberation of formaldehyde only occurs at acid pH values.

Acids

Inorganic acids are unimportant as disinfectants. For example, boric acid, which was previously used, is today obsolete (it is absorbed and has potentially lethal toxicity in children). Neither are the organic acids of particular importance. Salicylic acid has a specific indication for local application (keratolysis), but it cannot be described as a disinfectant. On the basis of its bacteriostatic properties, it is used, as is benzoic acid, as a preservative agent. Parahydroxybenzoic acid esters (i.e., methyl and propyl esters) have proved valuable as additives to drug preparations, cosmetics, etc., because of their inhibitory effect upon bacteria, molds, and yeasts. On the other hand, they can elicit allergic skin reactions. Mandelic acid can sometimes be used as a urinary disinfectant. Long-chain fatty acids such as caproic acid and undecenylic acid possess fungicidal activity. They are therefore used for topical therapy in preparations containing 2–10%.



Caproic acid



Undecenylic acid

Oxidizing Agents

The property common to oxidizing agents is the ability to liberate oxygen. As the result of its strong reactivity, oxygen oxidizes enzyme systems in the bacterial cells which must be in the reduced form for the life of the microorganism. A compound which liberates oxygen as the result of the action of catalase, which is present in all tissues and acts under physiological conditions as a peroxidase, is hydrogen peroxide (H_2O_2). It acts as a disinfectant and therefore as a deodorant.

Hydrogen peroxide is suitable for the washing of wounds and mucous membranes. In addition it can be used for the mechanical cleaning of wounds and loosely attached dressings. The disinfectant activity is transient; the depth of penetration is very small. A solution of 3% hydrogen peroxide diluted five to tenfold is used.

Potassium permanganate is a strong oxidizing agent that can be utilized in dilutions of 1:5000–1:2000 ($2–5 \times 10^{-4}$ gm/ml) to wash out wounds and mucous membranes. Along with the disinfectant activity, this compound has an astringent effect.

The use of chlorates (e.g., $KClO_3$, potassium chlorate) has been completely abandoned because of their high toxicity. They result in methemoglobin formation and hemolysis with hemoglobinuria and possible anuria. Prior to absorption, marked symptoms of gastrointestinal irritation occur.

Halogens

Iodine

Elemental iodine possesses bacteriocidal and fungicidal properties. The mechanism of action upon which the effect is based is unknown; it may be similar to that of chlorine. Iodine is used as a skin disinfectant, most suitably in alcoholic solution (the sterilization of surgical fields). A 2% solution of iodine is sufficient for disinfection (iodine tincture USP). The addition of potassium iodide serves to stabilize the solution. Alcoholic iodine solutions are not exceeded in effectiveness by any other disinfectant agent for preparation of operative fields because the activity is very good and sets in promptly. The iodine solution can be washed off with alcohol as soon as 5 min after its application. In this way, one avoids the entrance of iodine into the peritoneal cavity in cases of laparotomy and hinders the subsequent formation of adhesions. Another disinfectant agent should be used for the prescribed purpose only if there exists a hypersensitivity to iodine. A true hypersensitivity reaction with severe symptoms of shock, fever, and eruptions of the skin occurs extraordinarily seldom. On the other hand, the skin reacts more frequently to tincture of iodine with the formation of scales and blisters at the site of application.

The most prominent symptom following accidental, oral intoxication with tincture of iodine is irritation of the gastrointestinal tract. The diagnosis is more easily made because of the brown coloration of the mucous membrane of the mouth and throat. Circulatory collapse and renal damage can occur following intestinal absorption. Antidotes are sodium thiosulfate (10–20 gm by mouth) which reduces the elementary iodine to iodide ions, and starch which complexes iodine. Absorptive intoxication requires symptomatic therapy (possibly sodium thiosulfate intravenously).

Chlorine

Chlorine gas (Cl_2) has a very potent germicidal effect (a dilution of $1:10^7$ is lethal within 30 sec for a whole series of bacteria) that can be used for the disin-

fection of water. When chlorine is passed into water, one of the compounds produced is hypochlorous acid

$$Cl_2 + H_2O \rightarrow H^+ + Cl^- + HOCl$$

Hypochlorous acid in its undissociated form is strongly bacteriocidal; in addition it slowly decomposes with the release of an oxygen atom (nascent oxygen in contrast to molecular oxygen O_2) which is also germicidal. The disinfectant activity of chlorine is based upon the reaction in which the amino groups of proteins are transformed to chloroamino groups. Dilutions of chlorine of the order of 1:2,000,000 are sufficient for the sterilization of water (drinking water, swimming pools).

The use of chlorine gas or hypochlorous acid is restricted to the above applications. On the other hand, compounds which slowly and constantly release hypochlorous acid and thereby chlorine, have a much wider field of application. Chloroamines, for example, are hypochlorous acid-liberating compounds. They possess the general formula

or

Chloramine-T (*p*-toluenesulfone chloramide) has relatively good water solubility. It is used in 0.05–0.25% solution for application to mucous membranes (bladder and vaginal lavage, infections of the mouth). The concentration for disinfection of the hands is about 0.25–0.5% in salves or 5–10% in dusting powders. Halazone (*p*-(*N*,*N*-Dichlorosulfamyl) benzoic acid) is particularly useful for the sterilization of drinking water. With a dilution of 1:250,000, water bacteria are killed within 1 hr, i.e., one 4-mg tablet is sufficient to sterilize 1 liter of water.

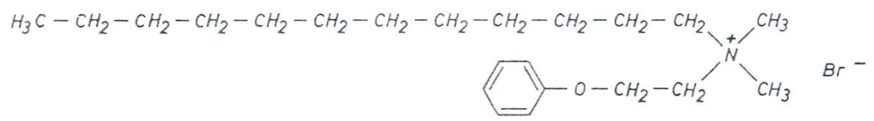
Surface-Active Agents (Detergents)

If a molecule contains hydrophilic and hydrophobic groups, it collects at interfaces in an ordered form and thereby influences the physical properties of these interfaces. Since cell membranes are composed of lipids and proteins, it is understandable that molecules with strong hydrophobic and hydrophilic groups are capable of changing the physicochemical properties of such membranes. Even if the mechanism of action is not known in detail, the most important effect appears to be an increase in permeability which results in the loss of enzymes, coenzymes, and metabolic intermediates. Those surface-active disinfectants utilized in medicine are also designated as invert soaps. This term originates in the following considerations: in so-called normal soaps the long-chain fatty acid exists as an anion, while with the surface-active agents the long-chain component occurs as a cation (cf. the formulas). Thus the relationships are inverted.

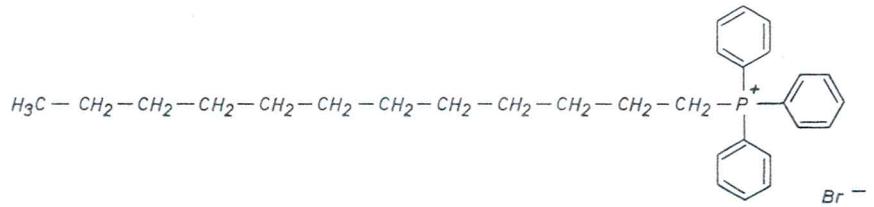
The invert soaps are used in concentrations of 1:20,000–1:1000 (up to 1:100), depending on the application. Many bacteria, especially the gram-positive ones, are destroyed with certainty; spores, fungi, viruses, and tubercle bacilli are not necessarily attacked. The activity is extraordinarily dependent upon the environment; an alkaline environment enhances the effect while soaps (anionic surface-acting agents) inhibit the activity. The invert soaps also lose their effect in the presence of serum, pus, protein, etc. The great advantage of this group of compounds is their low local and systemic toxicity.

The invert soaps are widely used for irrigating wounds and vaginal douches; they are of limited usefulness for disinfecting the hands. Sterile instruments can be kept in solutions of invert soaps provided that spores and fungi are prevented from entering the solutions. The following compounds have been found useful for these purposes: benzalkonium chloride (alkyldimethylbenzylammonium chloride; the alkyl chain is a mixture of $-C_8H_{17}$ to $-C_{18}H_{37}$) and domiphen bromide (cf. formula). An example of compounds which have instead of a quaternary nitrogen, a corresponding phosphorus atom in a hydrophilic nucleus is dodecyltriphenylphosphonium bromide, which apart from its antibacterial activity also possesses antimycotic activity and is therefore indicated in dermatomycoses. The amphotensides are similar in their activity to the invert soaps (i.e., 1-dodecyl-1,4,7-triazaoctan-8-carbonic acid-HCl).

Hydrophobic moiety — Hydrophilic moiety



Domiphen bromide
Dodecyldimethyl(2-phenoxyethyl)-ammonium bromide



Dodecyltriphenylphosphonium bromide

Heavy Metal Salts

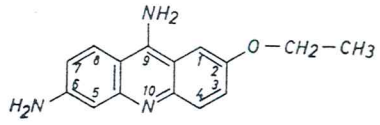
Formerly, mercury salts were of great importance as disinfectants. However, their therapeutic index is so small and the danger of absorptive poisoning so great that they have been completely abandoned (cf. mercury poisoning). Or-

ganically bound mercury has a lower local and systemic toxicity. Such compounds, themselves, and the slowly liberated mercuric ion have antiseptic activity. The mechanism of action rests upon the blockade of sulfhydryl group-containing enzymes. The disinfectant activity of organic compounds of mercury is not judged to be too favorable. Examples of compounds of this type are merbromin (2–7-dibromo-4-hydroxymercurifluorescein) and phenylmercuric nitrate. The latter is also used for its spermicidal effect.

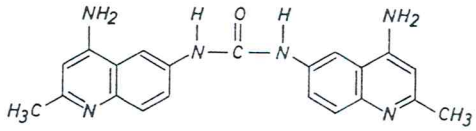
Silver in the form of silver nitrate has bacteriocidal activity along with an astringent and cauterizing effect. These can be used in combination with the protein precipitating activity for the treatment of certain forms of cystitis as well as in prophylaxis of opthalmia neonatorum or for the painting of infected rhagades of the mouth. Silver nitrate is also applied in very dilute solutions for the prophylaxis of infection in cases of burn wounds. Silver can be used as a protein–silver complex, which lacks the protein precipitant action. Such colloidal silver has almost no astringent effect.

Acridine and Quinoline Derivatives

Acridine derivatives have a good disinfectant action and are relatively nontoxic. These yellow dyes are particularly suitable for the treatment of infected wounds covered with moist dressings because they are especially active against pus-forming cocci. The same indications exist for the symmetrical quinoline derivative 1,3-



Ethacridine
6,9-Diamino-2-ethoxyacridine



1,3-Bis(4-Amino-2-methyl-6-quinolyl)urea

bis(4-amino-2-methyl-6-quinoyl) urea. The simpler quinoline derivative, *o*-hydroxyquinoline, is less effective. The acridine derivative, ethacridine, is used for local therapy, and is active in dilutions of 1:5,000–1:1,000 or in salve form of 1–5%. The exact mechanism of action of these compounds is unknown; there is some indication that they inhibit the terminal respiratory chain of microorganisms.

Halogenated hydroxyquinoline derivatives are still more effective. They are widely used in the prophylaxis and treatment of chronic intestinal infections.*

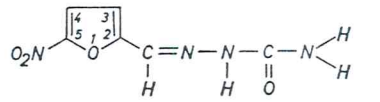
* These are Enterosept, Enterovioform, Intestopan, Mexaform, Mexase, and Sterosan.

These compounds can produce polyneuropathies and optic nerve atrophy after high doses or upon long-term administration. Particular attention should be paid to the dosage in children. One should be forcefully warned against the uncritical use of these compounds.

Furan Derivatives

The introduction of the nitro group into position 5 of the furan ring already substituted in position 2 produces compounds with bacteriocidal activity.

Nitrofurazone is bacteriostatic and bacteriocidal to gram-positive and gram-negative bacteria; it is devoid of fungicidal activity. The bacteriocidal effect is diminished in the presence of blood and pus. Its effects are not particularly marked in cases of *Proteus* and *Pseudomonas* infection. A disadvantage in nitrofurazone treatment is the tendency of the skin to develop hypersensitivity reactions in the course of a few days. Treatment with nitrofurazone should not be extended for



Nitrofurazone
5-Nitro-2-furaldehyde semicarbazone

longer than 8 days and should be restricted to small areas. A 0.2% solution is commonly used for local application.

Nitrofurantoin [*N*-(5-nitro-2-furfurylidene)-1-aminohydantoin], is well absorbed from the intestine. Since a large fraction is excreted unchanged by the kidney where it accumulates, it has found use in the disinfection of the urinary tract. One must expect a series of side effects, among others, peripheral neuropathies, particularly when its excretion is delayed as the result of renal damage. Allergic reactions with fever and severe pulmonary conditions have been reported.

Tolnaftate

This compound (*m*,*N*-dimethylthiocarbanilic acid *O*-2-napthyl ester) has good antimycotic activity. It can be successfully utilized in interdigital mycoses.

Insecticides

Only the modern contact insecticides will be discussed. In addition to their great importance in the fight against insects, they are of particular toxicological interest. One is concerned with the chlorine-containing compounds (chlorophenothane and hexachlorocyclohexane) and with the phosphoric acid esters. Common to both groups is the fact that they are taken up by the insects through their outer covering (chitin exoskeleton) and poison the nervous system.

Chlorophenothane (DDT)

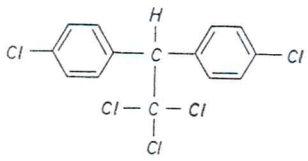
Chlorophenothane has a very marked insecticidal activity; the lethal dose is approximately 10^{-9} gm/gm of fly, which is equal to about 10^{-11} gm per fly. The amount of chlorophenothane which must be sprayed upon wall surfaces, etc., is correspondingly small—about 0.001 mg/cm^2. The contact of the legs of the fly with such a prepared surface results in the absorption of sufficient material to kill the fly. The rapidity with which death results following a period of excitation is dependent upon the quantity taken up; even with high doses this lasts for hours. The toxic effect probably results from a disturbance in ion permeability during the excitatory processes in nerves.

Along with flies and mosquitoes, human ectoparasites such as lice, fleas, and bedbugs are sensitive to chlorophenothane. For use against lice and fleas, a 5% power or a 0.2% emulsion for the impregnation of clothing is utilized. To eradicate bedbugs, a 5% solution must be sprayed upon walls, wall coverings, and furniture.

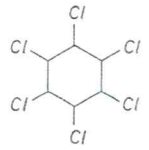
The acute toxicity of chlorophenothane is relatively low for mammals and man. This is in part because chlorophenothane is not absorbed from the skin and only very slowly from the intestine. Only when it is dissolved in an organic solvent does percutaneous absorption take place to a greater extent. Since chlorophenothane is poorly water soluble, but possesses good fat solubility, it is stored primarily in the fatty tissues of the organism. Excretion occurs in the course of months, primarily in the form of dichlorodiphenylacetic acid; thus chlorophenothane accumulates. Since it is excreted unchanged into the milk, one must be careful that cows do not receive forage containing chlorophenothane. Sometimes human milk contains chlorophenothane concentrations which cannot be tolerated.

The amounts of chlorophenothane which precipitate acute toxic symptoms in man are on the order of 10–20 gm by mouth (approximately 0.2–0.4 gm/kg; compare this value with the toxicity of chlorophenothane to insects). The amount ingested with food has considerably increased in the past few years. In nature, the compound is chemically stable. Owing to its lipid solubility, it is increasingly accumulated in the food chain, at the end of which stands man. The symptoms of toxicity are very unspecific. Even in animal experiments it can be demonstrated that higher mental achievements and behavior are primarily affected. More severe intoxications are accompanied by the following symptoms: fatigue, hyporeflexia, tremor, as well as convulsions, and finally coma and death occur. Chlorophenothane toxicity is augmented by a diet which results in a loss of fatty tissue.

In some countries the use of chlorophenothane has already been forbidden, particularly since natural bodies of water such as rivers and lakes, as well as sources of drinking water already have concentrations that are too high. (See also halogenated hydrocarbons.)



Chlorphenothane
1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane
(Dichlorodiphenyltrichloroethane = DDT)



1,2,3,4,5,6-Hexachlorocyclohexane

Hexachlorocyclohexane

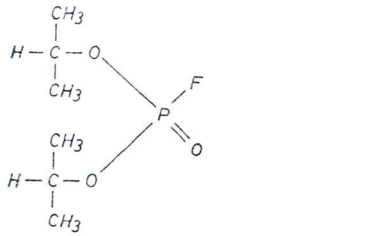
The γ isomer of this compound is, like chlorophenothane, a very active contact insecticide. The onset of the effect is more rapid than that following chlorophenothane and also consists of a transient excitation and consequent paralysis of the nervous system of insects. While the insecticidal activity of hexachlorocyclohexane is as potent as that of chlorophenothane, its toxicity for mammals also appears to be somewhat higher. Therefore, the internal use of hexachlorocyclohexane as an anthelmintic is contraindicated. Besides the indications for use which have already been discussed under chlorophenothane (eradication from living spaces and elimination of ectoparasites), hexachlorocyclohexane is a good antiscabies agent (0.3% emulsion).

The exact mechanism of action of hexachlorocyclohexane is not known. Neither is there an explanation why insects develop a resistance toward insecticides. Although convulsions occur with acute toxicity in warm-blooded animals, the ability to respond to convulsant agents is diminished for a long period of time. Apart from that, the chronic toxicity of the drug is comparable to that of chlorophenothane.

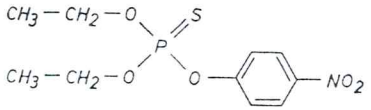
Phosphoric Acid Esters

The phosphoric acid esters are very toxic as a result of their cholinesterase-inhibiting properties. They are also absorbed percutaneously. Because of their systemic toxicity, they do not have a significant role in human therapy (with the exception of local application to the eye as an indirect parasympathomimetic). However, since the organophosphates possess very marked insecticidal activity, they have found wide application as insecticides for the protection of plants. For this reason they are of medical-toxicological interest since cases of intoxication of accidental, suicidal, and criminal origin are relatively frequent with the phosphoric acid esters.

The mechanism of action which determines the toxicity is relatively well known. The phosphoric acid esters are cholinesterase inhibitors. The degradation of endogenous acetylcholine is inhibited and the organism poisons itself. As explained in the section on the autonomic nervous system, acetylcholine is very rapidly hydrolyzed by cholinesterase when it reacts with the two active sites of the enzyme (cf. p. 11). The esteratic site reacts with the ester linkage of acetylcholine; this center is attacked by the phosphoric acid esters. One of the bonds to the phosphorus atom is so labile that the phosphate attaches itself to the enzyme with the cleavage of that bond (e.g., the F–P bond in DFP). Thereby, the esteratic site of cholinesterase is phosphorylated. The phosphorylation of this site corresponds



Diisopropylfluorophosphate
(DFP)



Parathion
O,O-Diethyl-O-p-nitrophenyl phosphorothioate

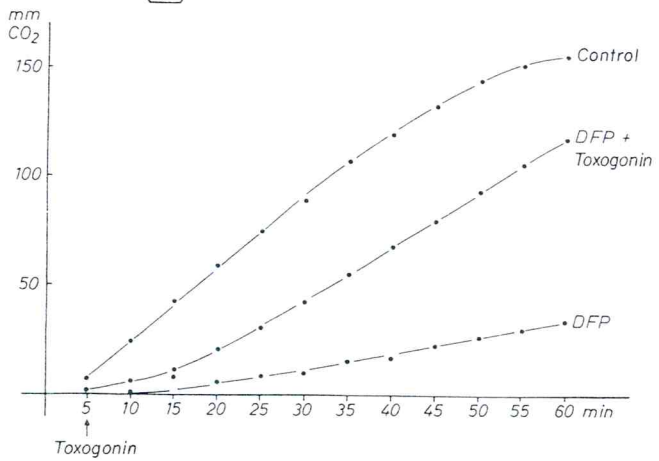


Fig. 54. Reactivation of DFP inhibited cholinesterase by toxogonin. Warburg manometric determination of acetylcholine hydrolysis. Control: hydrolysis of acetylcholine by true cholinesterase (guinea pig erythrocytes); DFP: inhibition of enzyme activity by the addition of diisopropylfluorophosphate $3 \times 10^{-6}M$ 30 min before the beginning of the experiment; DFP + toxogonin; reactivation of the DFP-inhibited esterase by addition of toxogonin ($10^{-4}M$) at the 5-min time point.

to the acetylation that occurs as an intermediate step in the enzymic hydrolysis of acetylcholine. It may also be compared with the carbamylation that occurs when the esterase is exposed to inhibitors of the physostigmine type. In contrast to the deacetylation, the dephosphorylation occurs slowly (see p. 13), so that irreversible damage to the enzyme is simulated in that this site is no longer available for acetylcholine hydrolysis. Acetylcholine is not capable of displacing the phosphate substituent from the enzyme. Therefore the organophosphates are noncompetitive inhibitors with regard to acetylcholine. Cholinesterase activity can

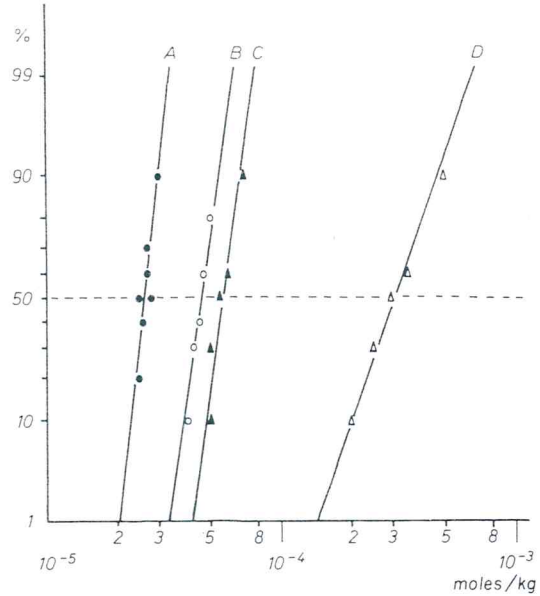
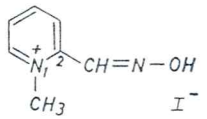


Fig. 55. Dose-mortality curves. Diisopropylfluorophosphate (DFP) was injected subcutaneously into mice. The dose is given on the abscissa in moles/kg in logarithmic units. The ordinate shows the percentage of animals in each group which died. Each point corresponds to a group of 10 mice. The ordinate is stretched in such a manner that the S-shaped curve obtained with a linear ordinate (cf. Fig. 62, p. 317) is transformed to a straight line. A, DFP toxicity (control); B, DFP toxicity after pretreatment with toxogonin (10 μmoles/kg subcutaneously); C, DFP toxicity after pretreatment with atropine (10 μmoles/kg subcutaneously); D, DFP toxicity after pretreatment with toxogonin and atropine (10 μmoles/kg each subcutaneously). Note the increase in the DFP dose at which 50% of the animals die (LD_{50}).

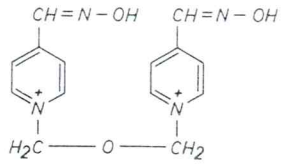
only be increased by physiological regeneration; thus 50 days are required for complete regeneration of brain cholinesterase and about 100 days for that of erythrocytes. The symptoms of toxicity, however, disappear when only a fraction of the normal enzyme activity is again available.

However, compounds have been found which possess an even greater affinity for the phosphoric acid esters than does cholinesterase. With them it is possible to reactivate the inhibited esterase (Fig. 54). Nevertheless the extent of the reactivation is dependent upon the duration of the contact between the inhibitor and the cholinesterase, as well as the chemical properties of the particular phosphoric acid ester. Following formation of the esterase-inhibitor complex, with some derivatives, alkyl moieties are split off ("aging"). This "aged" complex can then no longer be reactivated. There is the tendency to utilize as insecticides cholinesterase inhibitors which "age" slowly, while for chemical warfare compounds are developed which rapidly "age" so that reactivation following the occurrence

of intoxication is no longer possible. The positively charged nitrogen of the reactivators first binds to the anionic site of the esterase (cf. p. 11). Thereby the aldoxime side chain is placed directly in the neighborhood of the phosphorylated esteratic site. There now follows a transphosphorylation and regeneration of the cholinesterase. Typical cholinesterase reactivators are pralidoxime (PAM) and toxogonin.



Pralidoxime iodide
2-Pyridine aldoxime methyl iodide(2-PAM)
2-Formyl-1-methylpyridinium iodide oxime



Toxogonin
bis(4-hydroxyiminomethylpyridinium-1-methl) ether

In mammals and man poisoning with the phosphoric acid esters results from a flooding of the organism with endogenous acetylcholine. Correspondingly, the autonomic nervous system symptoms consist in the muscarinic and nicotinic effects of acetylcholine. An excess of acetylcholine also exists at the motor end plates, and the central nervous system as well shows signs of acetylcholine toxicity. The following symptoms are generated (according to the severity of the toxicity): parasympathetic stimulation with diarrhea, involuntary micturition, elevated glandular secretion (salivary and tear glands, etc.), bradycardia, sweating, miosis, and increased bronchial secretions with bronchoconstriction. The skeletal musculature exhibits fascicular twitching. Central nervous effects are expressed as convulsions and respiratory paralysis. Death results from pulmonary edema and central as well as peripheral respiratory paralysis.

Therapy for phosphoric acid ester poisoning requires (1) compensation with very large doses of atropine (daily doses 30–100– or up to 350 mg possibly for weeks if required) for the flooding of the autonomic nervous system with acetylcholine (Figs. 55 and 56), (2) artificial respiration, (3) the interruption of centrally elicited convulsions with depressant agents such as hexobarbital, (4) treatment of acidosis with tris buffer and $NaHCO_3$, (5) the symptomatic treatment of potential and existent pulmonary edema, and (6) a reactivation of cholinesterase (Figs. 54 and 55). The reactivators are not active against all slowly aging organophosphates. The symptoms of toxicity can even be potentiated in the case of some insecticides. In the absence of a successful response, the reactivators should not be further administered. Atropine must be given in every case.

There exists a large number of phosphoric acid esters with inhibitory activity on cholinesterase. In the collection of chemical formulas there are two typical representatives of the slowly aging type, namely, DFP and parathion. They are "relatively harmless" (1–2 mg/kg, lethal dose) compared to the chemical warfare agents which immediately age, such as soman (Methyl phosphonofluoridic acid 1,2,2-trimethylpropyl ester).

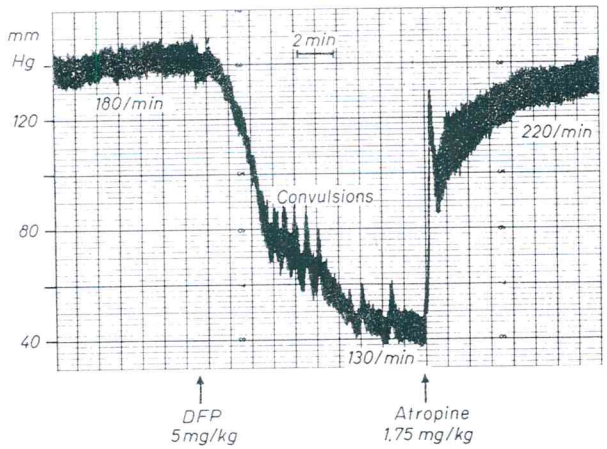


Fig. 56. The effect of atropine upon the blood pressure response to diisopropylfluorophosphate (DFP). The blood pressure of a cat was recorded by means of a pressure transducer. Atropine and DFP were injected intravenously. Following the administration of DFP, the blood pressure falls, the heart rate decreases, (values under the blood pressure tracing) and convulsions occur. The blood pressure and cardiac frequency are restored to normal after the injection of atropine.

There exist experimental findings which suggest that parathion itself is not the actual toxic compound. In the organism the divalent sulfur atom is replaced by an oxygen atom and thereby the active cholinesterase inhibitor, paraoxon (diethyl *p*-nitrophenyl phosphate) is produced.

Acaricides

The use of acaricides is restricted to the eradication of the species causing scabies, *Acarus scabiei*, a mite. As mentioned above, hexachlorocyclohexane is also an excellent agent against these pests. Just as good is the oily fluid benzyl benzoate, best used as a 25% lotion. Finally, the sulfur-containing mesulphen (2,6-dimethylthianthrene) can be used.

Antibiotics and Chemotherapeutic Agents

Shortly after the discovery of bacteria, experiments were begun in order to find agents with which bacteria could be killed or at least their growth inhibited. The first disinfectants or antiseptics such as phenols or corrosive sublimates had indeed the desired effect, but were only usable outside the living body since following parenteral administration the host was simultaneously damaged along with the

microorganisms. Only after consideration of specific metabolic pathways for each organism could progress be made whereby in the ideal case the metabolism of the cells of the host would not be disturbed at all. One now has a large number of chemical compounds with the desired properties which more or less fulfill this role. If they are chemically synthesized they are called chemotherapeutic agents; if they are primarily metabolic products of microorganisms, they are called antibiotics. It should be noted that the two groups do not differ basically in their action; i.e., both groups interfere somewhere in the metabolism of the microorganisms. If the further multiplication of the microorganisms is thereby inhibited, one speaks of bacteriostatic activity; if the microorganism is killed, one speaks of bacteriocidal activity. Generally it is of no importance if an agent also has bacteriocidal activity in higher concentrations because an inhibition of the multiplication of the microorganism generally is sufficient for the therapeutic effect. The infection is then overcome by the body's own defense mechanisms. However, should it be feared or established that surviving organisms remain active, bacteriocidal agents are indicated.

Chemotherapeutic agents and antibiotics can be divided into various groups on the basis of their mechanism of action.

1. Effect on the cell membrane.
   a. Interference with the synthesis of the cell wall: penicillin, cephalosporin, bacitracin, cycloserine.
   b. An increase in the cell membrane permeability (to be compared with detergents); polymyxin and the fungicidal compounds, nystatin, and amphotericin.
2. Inhibition of protein synthesis: tetracyclines, chloramphenicol, streptomycin, kanamycin, neomycin, erythromycin.
3. Interference with important metabolic steps: sulfonamides, *p*-aminosalicylic acid.

Understandably those compounds which affect the cell membrane are bacteriocidal, while those drugs which inhibit protein synthesis and other metabolic steps are bacteriostatic. Furthermore, it can be deduced from the various mechanisms of action that those antibiotics interfering with the synthesis of the cell wall only have activity against multiplying cells. Simultaneous therapy with bacteriostatic agents (e.g., tetracyclines) interferes therefore with the activity of other groups (e.g., penicillin). On the other hand, compounds with similar mechanisms of action can mutually potentiate their effects.

Along with this general grouping, it is necessary to take into account the specificity of the single drugs. For example, penicillin is primarily active against gram-positive bacteria (additionally on gram-negative gonococci and meningococci) and spirochetes; on the other hand, isoniazid is active only against tubercle bacilli. In contrast to penicillin, which can affect only a few types of microorganisms and isoniazid which affects only a single microorganism, there are antibiotics that can inhibit a large number of infectious species—e.g., the tetracyclines. They are therefore called broad-spectrum antibiotics. Within the last decade so many drugs

have been obtained that it is possible to successfully treat almost all classical infectious diseases, with the exception of virus infections. Unfortunately, this treatment has led to the appearance of new forms of infectious organisms which earlier were of little importance. This results from microorganisms whose metabolism is not affected by the chemotherapeutic agents or from those which have developed resistance. Therefore it will always be necessary in the future to discover and develop new therapeutic agents.

General Considerations for Treatment with Antibiotics and Chemotherapeutic Agents

Assessing the Practical Usefulness of Antibiotics

The antibacterial activity as well as the specific effects upon certain organisms can be determined *in vitro*. Thus, the concentration of drugs just sufficient for an inhibitory or lethal effect upon the organism is determined. This "minimal inhibitory concentration" is compared to the necessary drug concentration *in vivo*. In order to obtain the latter value, the behavior of the drug with regard to uptake, absorption, excretion, rate of inactivation, and penetration into diseased tissue should be taken into account. Furthermore, the degree to which the drug is bound to plasma proteins is of decisive importance since only the free fraction is available for antibacterial activity. Even within a group of closely related compounds, the degree of binding to plasma proteins can be considerably different (cf. penicillin, p. 278). A further limiting factor is the toxicity of the drug. Only those compounds are useful in practice in which the active concentration *in vitro* is smaller than that achievable *in vivo*.

There are also cases in which it is not possible to perform an *in vitro* determination of antibacterial activity, because the actual active compound is produced *in vivo* from the parent compound. The chemotherapeutic effect can then only be determined in animal experiments. Precisely the first chemotherapeutic agents belong to such a group, for example, the first antisyphilitic agent, arsphenamine, and the first sulfonamide, Prontosil. On the other hand, all antibiotics are active *in vitro*.

Synergism

The assumption that a combination of two antibiotics must produce a synergistic effect is generally not correct. In some cases it can even be demonstrated that a more or less marked antagonism exists between two antibiotics. Practically, combinations are of little importance (however, cf. p. 274 and p. 290). Frequently combinations of antibiotics are falsely considered to exhibit potentiation instead of addition. For potentiation, the effect of both drugs must be greater than would be expected from an addition of the effects of each agent (cf. p. 326). In principle, preparations containing two antiinfectious agents should not be used, since the fixed ratio between the doses does not allow consideration of the specific sensitivity of the bacteria in question. Thus, the danger of a toxic side effect is enhanced.

Development of Resistance

There are not only species of bacteria which are primarily resistant to an antibiotic on the basis of their particular metabolism, but also those which become resistant after being in contact with an antibiotic for a certain length of time. This is usually not because the entire population of the strain develops resistance by mutation, but is rather due to the selection of individual organisms that have a primary resistance and can multiply unrestrained by any competition. This phenomenon is more frequently observed with antibiotics (e.g., staphylococcus against penicillin), but it also occurs with chemotherapeutic agents (e.g., gonococci against sulfonamides). The resistance of staphylococci to penicillin can be explained by the production by these organisms of an enzyme, penicillinase, which destroys penicillin. Resistance to streptomycin which develops after a single or a few injections is probably ascribable to a mutation.

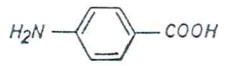
Changes in the genetic material of bacteria can also occur by a parasexual mechanism, i.e., a transfer of genetic information from cell to cell. Also in such cases the development of resistant strains through the influence of the added selective pressure of the chemotherapeutic agent must be feared. Finally, an infectious resistance is possible in which the resistance (R)-factor is transferred from cell to cell. For example, multiple resistance factors from nonpathogenic *E. coli in vivo* are transferred to salmonella or shigella so that these latter organisms are then resistant to several chemotherapeutic agents.

Sulfonamides

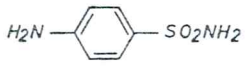
Sulfonamides used as chemotherapeutic agents are derivatives of sulfanilamide. It was found that the first compound of this group utilized in therapy, Prontosil, liberated the active material sulfanilamide in the body. It was additionally shown that the activity of sulfanilamide could be considerably increased by substitution of the amide group. The introduction of a heterocyclic ring, particularly pyrimidine, was effective. While a comparison of the spectrum of activity of these sulfonamides with one another shows no remarkable variation, there are considerable differences in the solubility, absorption, and rate of excretion of the individual agents. These differences can be exploited in therapy.

With further changes in the sulfonamide molecule which resulted in loss of antibacterial activity, compounds were produced which exhibited completely new effects, i.e., oral antidiabetics, carbonic anhydrase inhibitors, or saluretics, as well as compounds which block secretion in the renal tubules (probenecid).

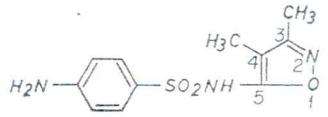
From the very large number of synthetic sulfonamides, only the most important are discussed here.



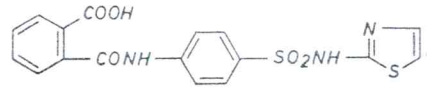
p-Aminobenzoic acid



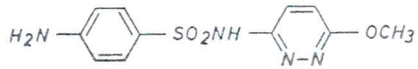
Sulfanilamide
p-Aminobenzenesulfonamide



Sulfisoxazole
N¹-(3,4-Dimethyl-5-isoxazolyl) sulfanilamide



Phthalylsulfathiazole
4'-(2-Thiazolylsulfamyl) phthalanilic acid
(Poorly absorbed)



Sulfamethoxypyridiazine
N-(6-Methoxy-3-pyridazinyl) sulfanilamide
(Long-acting preparation)

Mechanism of Action of Sulfonamides

All sulfonamides exhibit their bacteriostatic activity also *in vitro*. *p*-Aminobenzoic acid is required by some bacteria for growth in that it is necessary for the formation of folic acid (cf. formula, p. 83). As the result of their chemical similarity to *p*-aminobenzoic acid, sulfonamides occupy the reactive sites so that the synthesis of folic acid necessary for the multiplication of bacteria is inhibited (Fig. 57). Only if bacteria have no requirement for folic acid or do not carry out folic acid synthesis are they resistant to sulfonamides. Animal cells do not synthesize folic acid and therefore this compound must be obtained from exogenous sources as a vitamin. For this reason, a disturbance in the basic function of such cells is not to be expected during sulfonamide therapy.

Uptake and Distribution

Most sulfonamides used for oral therapy are rapidly and completely absorbed from the gastrointestinal tract. A maximal blood concentration is achieved within 4 hr following sulfisomidine and 2 hr after sulfisoxazole. Some sulfonamides are practically not absorbed at all. They are deliberately used in bacterial infections of the intestinal tract for their local bacteriostatic effect. Sulfaguanidine and phthalylsulfathiazole are members of this group. With the latter compound, the amino moiety is first set free in the intestine.

The blood concentrations are dependent upon the dose and the rapidity with which the drug is eliminated. Although sulfonamides are found in all body fluids, there are demonstrable differences between the various compounds depending mainly upon the extent of their binding to plasma albumin. The bound fraction is not ultrafilterable, is not bacteriostatic, and does not pass into the cerebrospinal fluid. Since only a given fractional amount of the sulfonamide is bound to protein, it is released from its combination with protein as the unbound drug is eliminated by the kidney.

A further fraction, quantitatively different for each sulfonamide, is acetylated

in the body, primarily in the liver. This acetylation occurs on the amino group. These products are devoid of bacteriostatic activity. For practical use, those drugs are preferred in which the fraction which is not bound to protein and not acetylated is as high as possible.

Blood concentrations of the order of 70 mg/liter are bacteriostatic, with more certain effects at 100–150 mg/liter. One should take into consideration the fact that because of anatomical peculiarities the concentration at the site of infection may not reach that in the blood.

Excretion

The sulfonamides are completely excreted by the kidney. They are not only filtered but also in part subject to active tubular secretion. Thereby, a considerable concentration of the sulfonamide or its acetylation product can occur in the urinary ducts, with severe consequences under certain conditions (see the next section). The rate of excretion for the various compounds in this group is very different. With those sulfonamides first introduced into therapy, the excretion was so rapid that in order to maintain a stable blood level, administration every 4–6 hr was required. In contrast, those sulfonamides with a longer duration of action used at present are so slowly excreted by the kidney that following an initial dose of 1–2 gm, a bacteriostatic blood level can be maintained with a daily dose of 0.5–1 gm. With such slow excretion, the possibility of accumulation must be taken into account (poor manageability). Following the appearance of dangerous side effects, the long persistence of the compound in the body can be disadvantageous.

Side Effects

Generally, the side effects are slight and do not require the interruption of treatment. However, since some dangerous and possibly life-threatening side effects can occur, every patient should be carefully observed during a course of therapy. Side effects occasionally occurring are gastrointestinal complaints, nausea, vomiting, as well as dizziness, headache, and even psychic alterations.

A very important but generally avoidable toxic effect results from the concentration of the drug in the urinary ducts as mentioned above. Many sulfonamides and their acetylation products are poorly soluble in urine, particularly at an acid pH. When the urinary filtrate passes through the tubules, there can be a precipitation of crystals as the result of the concentration and acidification of the urine at these sites. These sulfonamide crystals can block the renal tubules and the ducts of the pelvis, resulting in the development of hematuria, oliguria, and finally anuria. This very serious complication can be avoided if relatively good water-soluble compounds such as sulfisoxazole and sulfisomidine are chosen. In addition, one should strive for the production of large amounts of urine and the urine should not be allowed to become strongly acid. Newborn children should not be treated with sulfonamides since kernicterus may develop (see also p. 333). Moreover, under certain circumstances methemoglobin formation and hemolytic

anemia may occur. Besides these toxic side effects, which are primarily dose dependent, numerous effects which are primarily of an allergic nature can occur. Exanthema of varying size and appearance on the skin and mucous membrane with or without fever may develop. Although granulopenias are not so rare, agranulocytosis and severe liver damage are observed only very rarely. Agranulocytosis occurs generally between the tenth and twenty-first day of treatment, fever on the seventh to ninth day.

Although the allergic nature of the above side effects is by no means established in all cases, one frequently observes sensitization toward sulfonamides occurring especially after topical application. For this reason this mode of application should be avoided as far as possible. It should be noted that a negative skin test is no guarantee that a sulfonamide allergy is not present.

The side effects of the long-acting sulfonamides are more pronounced than those of the classical compounds. While the usual sulfonamides disappear rapidly from the body following interruption in treatment because of the appearance of side effects, this is not the case for the long-acting sulfonamides. On the contrary, as the result of the delayed excretion, there exists a chronic and possibly dangerous drug reaction. Along with the known disturbances, very severe, sometimes lethal, reactions have been described: bullous or exfoliative dermatitis, Stevens-Johnson syndrome, hemolytic or aplastic anemia, thrombocytopenic purpura, and psychosis. Combination with oral antidiabetics (of the sulfonamide type) can be dangerous. The "super long-lasting sulfonamides" now under investigation should be carefully examined in light of the foregoing precautions.

Indications and Use

Sulfonamides should not be used if penicillin is effective. Infections with *E. coli* and bacterial infections of the intestine can still be treated with sulfonamides. An exception is the use of these drugs in the prolonged prophylaxis of rheumatic diseases, if penicillin is not well tolerated. In ulcerative colitis salicylazosulfapyridine (5-[*p*-(2-Pyridylsulfamoyl) phenylazo] salicylic acid) has been shown to be valuable in that it accumulates in the submucosa of the colon. The chronic bronchitis of emphysema can be favorably affected by long-term sulfonamide administration. For this purpose the long-acting sulfonamides are suitable, i.e., sulfameter or sulfamethoxypyridazine.

Sulfonamides are frequently given without a clear diagnosis of the complaint. They are not indicated in cases of influenza, measles, colds, infections caused by anaerobic streptococci or enterococci, brucellosis, or acute rheumatoid arthritis and in local therapy. The dosage schedule is worked out on the basis of the rate at which the various compounds are excreted. For compounds with an intermediate duration of action, 4–6 gm daily by mouth is appropriate (e.g., with sulfisoxazole or sulfisomidine). The single dose of 1 gm must be given every 6 hr, or every 4 hr in cases of severe infection. The initial dose is double or three times the maintenance dose. With long-acting sulfonamides, the initial dose is 1 gm once per day by mouth, later reduced to 0.5 gm per day. In severe infections the dose should be doubled, but attention should be paid to the possible appearance of symptoms of accumula-

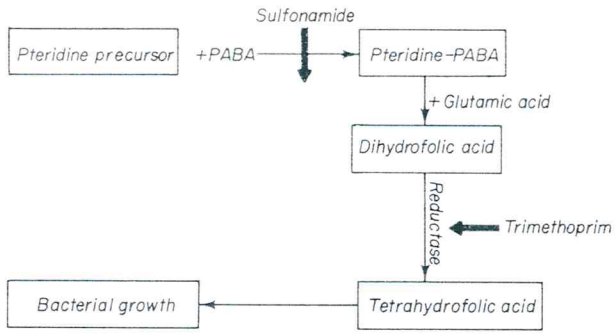


Fig. 57. Schematic representation of the synthesis of folic acid and its reduction to tetrahydrofolic acid. This reduction is also essential for mammals. The sites of action of the sulfonamides and trimethoprim are shown, PABA = *p*-aminobenzoic acid.

tion. In all cases of sulfonamide therapy, the dosage schedule should be carefully adhered to; scattered doses are useless.

Trimethoprim (2, 4-diamino-5-[3, 4, 5-trimethoxybenzyl]-pyrimidine) inhibits dihydrofolic acid reductase and thus impairs the formation of the tetrahydrofolic acid that is required for the synthesis of bacterial proteins (Fig. 57). If trimethoprim is combined with a sulfonamide (sulfamethoxazole) which inhibits the synthesis of folic acid in an earlier stage, frequently better effects may be achieved than with a sulfonamide alone ("sequential effect"). Particularly in cases of bronchitis or pyelonephritis that are more or less resistant to treatment, this combination frequently seems to be useful; it may also be useful in infections with salmonella typhi (in treatment of patients that chronically excrete these bacteria without showing symptoms of the disease). It should be taken into consideration that in contrast to the sulfonamides, trimethoprim interferes with a site in folic acid metabolism which is also of importance in humans.

Penicillins

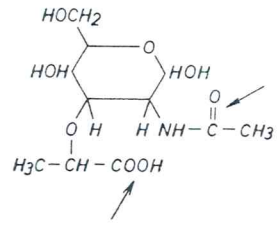
Penicillin is an antibiotic occurring in various forms that has been obtained from the culture medium of certain strains of mold, e.g., *Penicillium notatum*. The various forms were initially differentiated from one another by alphabetic letters, i.e., penicillin G = benzylpenicillin. Although the chemical synthesis of penicillin has been achieved, the original method of manufacture has not been abandoned for economic reasons. 6-Aminopenicillanic acid can be obtained from cultures of *Penicillium chrysogenum*. This compound is the starting material for the synthesis of numerous penicillins with particular properties.

Antibacterial Activity of Penicillin

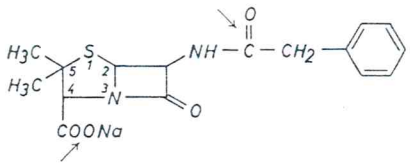
Penicillin G (called penicillin in the following discussion as it is the chief representative of the penicillin group) inhibits the growth of numerous microorganisms.

It is particularly active against gram-positive bacteria, especially streptococci, pneumococci, clostridia, and anthrax. It is also active against some gram-negative organisms, such as gonococci and meningococci while most other gram-negative organisms are not affected, i.e., *Escherichia coli*, *Proteus*, *Pyocyaneus*, *Salmonella*, and *Shigella*.

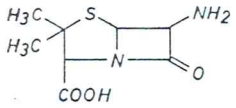
Staphylococci, which initially responded well to penicillin, have become less sensitive to an increasing degree or even completely resistant. Gonococci are slowly becoming less sensitive. *Streptococcus faecalis* is affected only at very high concentrations. Various spirochetes, such as *Treponema pallidum* (syphilis), *Treponema virenti* (Plaut-Vincent angina), *Treponema pertenue* (yaws), *Treponema*



N-Acetylmuramic acid; a component of the bacterial cell wall



Sodium benzylpenicillin, sodium penicillin G
(Arrows indicate the groups common to N-acetylmuramic acid)



6-Aminopenicillanic acid

borrelia (relapsing fever) respond well, while the leptospira, if at all, are affected only at the beginning of the infection and by very high doses. Diphtheria bacilli are inhibited in their development by penicillin, but the clinical progress of the disease is barely changed because it is a reflection of the effect of the toxin already released into the body which is not affected by penicillin. Penicillin is not active against viruses, rickettsia, tubercle bacilli, protozoa, and molds.

Sensitive organisms are inhibited by a penicillin concentration of 100 IU per liter blood and less. It is certainly possible with the usual procedure of penicillin administration to achieve blood levels of 100–1000 IU per liter; however, for longer periods of time this is possible only with depot preparations. An amount of 1000 IU corresponds to 0.6 mg of penicillin G of an international standard preparation; thus 0.6 gm is 1 million units (1 mega unit). Therefore the absolute amount of penicillin introduced into the body is relatively small.

Mechanism of Action of Penicillin

Penicillin has no effect on the metabolism of resting bacteria. It is bacteriostatic in that it inhibits the growth of organisms. It can also act as a bacteriocidal agent if the bacteria are multiplying rapidly under especially favorable conditions, i.e., in blood and tissue. In low, almost bacteriostatic concentrations, morphological changes in the bacterial wall, swelling, deformation, and lysis of the wall can be observed. Almost half of the basic structure of the cell wall of gram-positive bacteria consists of mucopeptides which in turn contain as their most important component *N*-acetylmuramic acid. It is very probable that owing to its similar chemical structure, penicillin acts as an inhibitor of the incorporation of *N*-acetylmuramic acid into cell wall mucopeptides. The morphological changes mentioned above are a result of this disturbance in synthesis. The gram-negative bacteria contain only very small quantities of muramic acid-containing mucopeptides in their cell wall. This probably explains the higher resistance of these bacteria to penicillins. Since *N*-acetylmuramic acid does not play a role in the formation of cell membranes in warm-blooded organisms, the lack of penicillin toxicity is easily understood. Bacteria with marked penicillinase activity exhibit various degrees of insensitivity to the classic penicillins.

Absorption and Excretion of Penicillin G and Depot Penicillin following Injection

For a number of years only two penicillins were used therapeutically: penicillin G (benzylpenicillin) and procaine penicillin. Both were injected intramuscularly. Penicillin G is rapidly absorbed and for this reason achieves a high blood level which, however, is maintained for only 3–4 hr with the usual doses because the compound is so rapidly excreted by the kidney (Fig. 58).

Within several hours 90–100% of injected penicillin or its metabolites is recovered from the urine. This excretion occurs as the result of active secretion by the renal tubular epithelium. This process can be retarded by some sulfonamides, in particular by probenecid. The latter compound competitively displaces the penicillin in the secreting tubular epithelium because both compounds are excreted via the same mechanism. This possibility of maintaining a high penicillin blood level for longer periods of time is currently used only in cases in which an excessively high penicillin level is required, i.e., by relatively resistant staphylococci or in subacute bacterial endocarditis.

In most cases the constancy of a therapeutically active penicillin level is achieved by injecting a large amount of penicillin which can be absorbed only slowly from the depot (depot penicillin). Such depot preparations are very poorly water soluble. For further retardation of the absorption rate, some preparations are dissolved in oil. Depot penicillins have the advantage that their activity is maintained for 8–24 hr depending upon the dose (procaine penicillin), or even for weeks as is the case with the proper doses of benzathine penicillin G. Precisely because of their slow absorption, depot penicillins alone often do not achieve an adequate blood level rapidly enough for use in acute infections. Also, with relatively penicillin-

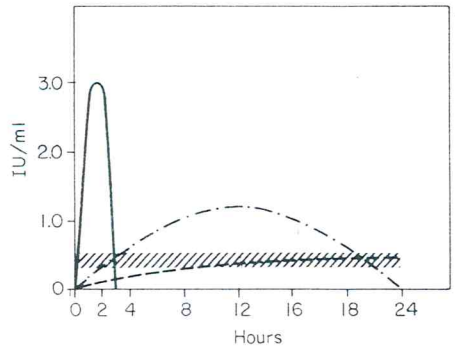


Fig. 58. Schematic representation of penicillin blood levels after the intramuscular injection of 100,000 IU of penicillin G (——), 300,000 IU of procaine penicillin G (·-·-·-), or 300,000 IU of benzathine penicillin G (----); necessary therapeutic blood levels for sensitive organisms (/////).

insensitive organisms, the achieved blood levels are often generally too low. In such cases it is necessary to combine depot preparations with penicillin G.

Absorption of Penicillins after Oral Administration

Following oral administration of penicillin G, only a small fraction appears in the blood. The largest part is destroyed in the gastrointestinal tract. Therefore this mode of administration requires doses eight to ten times higher than those for intramuscular injection. Phenoxymethyl penicillin (penicillin V) is somewhat more resistant to the hydrochloric acid in the stomach. Nevertheless penicillin V possesses no major advantage over penicillin G. Better orally effective penicillins are benzathine penicillin G, phenethicillin (phenoxyethyl penicillin), propicillin (phenoxypropyl penicillin), and ampicillin. Parenteral administration is still to be preferred in all cases of serious infection since there remains uncertainty as to the effective absorption of the penicillins by the oral route. This is true even for ampicillin.

Topical Application of Penicillin

It is useless to apply penicillin topically to wounds, to the mucous membrane of the mouth or the skin. If the use of penicillin is indicated, parenteral or oral administration is more effective. In addition, with each application to the skin or mucous membranes, there is an increased danger of sensitization. The same is true for the administration of aerosols, although in this way the same blood levels are achieved as following intramuscular injection.

Following spinal administration in meningitis, penicillin disappears from the cerebrospinal fluid very slowly. Therefore if at all, at most 10,000 IU in very high dilution may be injected at 12-hr intervals in order to avoid severe neurotoxic damage which is the single toxic (not allergic) effect that is caused by penicillin

(cf. below). Intrapleural or intraarticular injections can be given in addition to general therapy.

Behavior of Penicillin in the Body

Penicillin distributes itself evenly within the extracellular space. It passes into the fetus but does not penetrate into the brain, nerves, and bones. Under normal conditions following moderate doses, it does not diffuse to any appreciable extent into the cerebrospinal fluid, the aqueous or vitreous humors, or into joints. On the other hand, the permeability to penicillin is increased with inflammatory changes in these tissues. Following very high doses, i.e., 10–20 million IU daily, or after inhibition of renal penicillin excretion by probenecid, the blood levels increase to

TABLE X

The Fraction of Various Penicillins and Cephalosporins not Inactivated by Binding to Plasma Proteins (Estimates)

	Unbound fraction (%)
Ampicillin	80–90
Methicillin	50–70
Penicillin G	40–60
Penicillin V	40–50
Phenethicillin	30–40
Propicillin	~15
Oxacillin	5–12
Cloxacillin	5–10
Dicloxacillin	2–5
Cephaloridine	~23
Cephalothin	~62

100–300 IU per milliliter of serum. Under such conditions the passage of bacteriostatic quantities of penicillin into the cerebrospinal fluid can be expected. A certain fraction of the penicillin is inactivated by binding to plasma albumin. Since only free, unbound penicillin is active as an antibiotic, it is important to take into consideration the extent of protein binding for each single penicillin preparation. As can be seen in Table X, these values differ from one another considerably. All penicillins which are bound to an extent of more than 50% would seem to be less favorable; ampicillin is the best penicillin in this regard. After treatment of the mother, penicillin is found in fetal blood and in the maternal milk, although in lower concentrations than in maternal blood.

Penicillins Resistant to Penicillinase

Various microorganisms (e.g., some strains of staphylococci) contain the enzyme penicillinase, which hydrolyzes the lactam ring of penicillin (penicillin-β-lactamase-1). This results in the loss of penicillin activity. Penicillinase activity can be

markedly increased in the presence of penicillin as the result of enzyme induction. As a result, the therapeutic situation deteriorates. In this case even intrinsically sensitive organisms are not affected by penicillin. Chemical modifications of the penicillin molecule have resulted in certain compounds which are not destroyed by penicillinase i.e., methicillin (2,6-dimethoxybenzyl penicillin). This compound is about 100 times less potent than penicillin G. Very high doses are required, resulting in very expensive therapy. Methicillin is inactive by mouth. Occasionally, chemotherapeutic activity can also be achieved against "relatively resistant" staphylococci by very high doses of penicillin G.

Oxacillin is similar to methicillin but possesses better activity against "resistant" staphylococci. It can be given orally. Those compounds substituted with chlorine in the orthoposition on the phenyl ring of oxacillin (cloxacillin or dicloxacillin) are qualitatively simliar to the parent compound. Oxacillin and methicillin are excreted by the kidneys as rapidly as penicillin G.

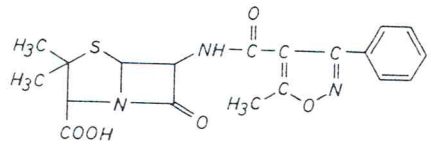
Penicillins with Broad-Spectrum Activity

Ampicillin is very easily destroyed by penicillinase, but in contrast to the earlier penicillins, it is also active against some gram-negative organisms. It is effective by the oral route. This interesting development promises further possibilities although at the present time the broad-spectrum antibiotics have not been replaced. Carbenicillin (carboxybenzylpenicillin) has the same antibacterial spectrum as ampicillin. Additionally, it is effective against *Pseudomonas aeruginosa* and against some strains of *Proteus*. It is ineffective when given by mouth.

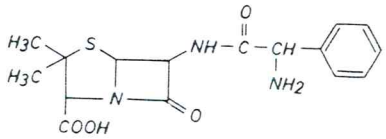
Side Effects

Even following large parenteral or oral doses of penicillin, no toxic side effects need be feared. Only excessively high doses, i.e., 20–30 million IU of penicillin G, can produce neurotoxic effects: confusion, hallucinations, muscle twitching, epileptiform convulsions, coma, and eventually death. In addition, penicillin damages the central nervous system following intraspinal or intracisternal injection. Motor and sensory disturbances of various types occur which are in part irreparable. On the other hand, penicillin allergy can occur. This is the case of an allergy which extends itself to all the penicillins. Caution is called for with repeated injections; the patient must always be asked concerning tolerance to earlier penicillin therapy. However, now and then even the first injection may result in a violent reaction, probably because sensitization has already occurred by exposure to molds or dermatomycoses. The form of the allergic reactions ranges from mild eruptions of the skin and urticaria to symptoms of serum sickness or anaphylactic shock. Following methicillin, damage to the bone marrow has also been reported. Allergy development occurs particularly easily following local application to the skin and mucous membranes. Therefore, this mode of application should be avoided entirely. With the use of procaine penicillin, sensitivity may occur not only toward penicillin but also toward procaine. In the latter case penicillin therapy can be continued with a procaine-free preparation. Following parenteral administration

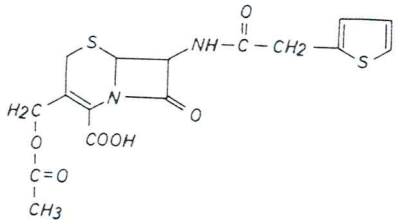
of very high doses of potassium-containing penicillin preparations, such as in the therapy of subacute bacterial endocarditis, symptoms of potassium intoxication can occur. In these cases sodium salts of penicillin must be utilized.



Oxacillin
5-Methyl-3-phenyl-4-isoxazolylpenicillin



Ampicillin
D-(−)-α-Aminobenzylpenicillin



Cephalothin

Indications and Usage

Penicillin is the drug of choice in all infections caused by penicillin-sensitive organisms (see the section on antibacterial activity). Even with relatively insensitive organisms, i.e., some staphylococci, it is frequently better to administer penicillin in large doses than to use another antibiotic with more marked side effects. The oral route should be avoided in all severe cases; in order to achieve a high blood level more rapidly, penicillin G should be injected intramuscularly at intervals of 3 hr day and night preferably in combination with a depot preparation given at intervals of 12–24 hr. The usual daily dose of penicillin G lies in the range of 1 million IU; with depot penicillins between 0.6 and 1 million IU; for therapy with extremely high doses (more than 10 million units per day) intravenous infusion with the corresponding amount of penicillin is recommended.

Under certain circumstances with infections by insensitive staphylococci, and with subacute bacterial endocarditis, daily doses of 20–100 million IU are necessary. Preparations with a longer duration of action are in use for the treatment of syphilis. They are administered at intervals of 2–4 days, i.e., depot penicillin with aluminum monostearate in an oil suspension. Seven intramuscular injections of 1.2 million IU each are sufficient for simple syphilis therapy. Sometimes higher doses are

given over a longer period of time. Preparations with an even longer duration of action are also suitable for the treatment of lues and the prophylaxis of rheumatic fever (cf. p. 144), i.e., benzathine penicillin G, the activity of which is maintained for 3–4 weeks following intramuscular injection of 1.2 million units.

Oral preparations should only be used in those cases in which possible failure of treatment as the result of too low a penicillin blood level does not carry with it the increased risk of more serious illness. The degree of binding to plasma protein by the various compounds should be taken into consideration in setting the dosage schedule (Table X). Simultaneous oral administration of probenecid is helpful in retarding the rapid excretion of penicillin. A combination preparation of penicillin with streptomycin which is frequently utilized in practice is not rational since the less toxic tetracyclines are more effective in such mixed infections and the organisms usually responsible in these cases are generally not sensitive to streptomycin.

Cephalosporins

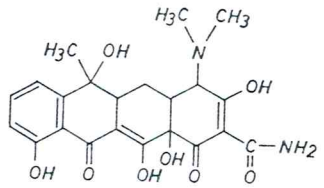
Various compounds with antibiotic activity have been isolated from the fungus *Cephalosporium*. These cephalosporins are closely related to the penicillins. Two semisynthetic antibiotics, cephaloridine and cephalothin, have been obtained by modification of the native molecule. The spectrum of activity is essentially that of penicillin. They are not absorbed following oral administration and are excreted by the kidneys as rapidly as penicillin G after parenteral administration, i.e., in a few hours. They are barely attacked by the usual penicillinases although destruction by a β-lactamase-2 which attacks both cephalosporins and penicillin can occur. Indications for their use are the same as for penicillin. In the presence of a penicillin allergy, the cephalosporins can usually be utilized as substitutes without injury. Nevertheless, cross allergies and even anaphylaxis do occur. The dose of cephalothin is about 1–2 gm intramuscularly or intravenously (over 5–10 min) every 4–6 hr. Cephaloridine results in renal necrosis in daily doses of more than 4–6 gm; cephalothin is less nephrotoxic and more active against penicillinase-producing staphylococci. Cephalexin is effective when given by mouth, although less potent. It shows the same spectrum of antibacterial activity but it is less nephrotoxic.

Tetracyclines

Antibiotics which are closely related chemically have been isolated from species of *Streptomyces*: tetracycline, chlortetracycline, oxytetracycline, doxycycline (deoxyhydroxytetracycline), and demeclocycline. Their activity is essentially the same.

These compounds are active by mouth. They are not very toxic. Their bacteriostatic activity extends to all organisms which are inhibited by penicillin as well as *Escherichia coli*, *Hemophilus influenza*, *Pasteurella tularensis*, and to a lesser extent *Klebsiella pneumoniae*. In addition, the tetracyclines are active in

shigella infections, brucellosis, rickettsiosis, lymphogranuloma venereum, trachoma, psittacosis, and even with amebic infections. With gonorrhea and syphilis, they possess sufficient activity but are weaker than penicillin. Only in exceptional cases are infections with *Proteus vulgaris* or *Pseudomonas aeruginosa* favorably influenced. The tetracyclines are considered to be broad-spectrum antibiotics because of their particularly wide range of activity. They impair protein synthesis in that they prevent the binding of the transfer RNA to the messenger RNA-ribosome complex. More and more tetracycline-resistant organisms have emerged with the passage of time. For example, a large number of strains of staphylococci are resistant to all tetracyclines.



Tetracycline

Behavior in the Organism

The tetracyclines are rapidly absorbed from the gastrointestinal tract. Since this absorption is retarded by calcium, metaphosphate is sometimes added to the preparation to prevent this effect of calcium. Iron also prevents enteral absorption. Ingestion of 0.25 gm of a tetracycline preparation by mouth once every 6 hr causes a slow rise of the blood level within 24 hr to several milligrams per liter which is usually sufficient for bacteriostatic effects toward sensitive organisms. Binding to plasma proteins is anywhere from 20 to 80%, depending upon the compound in question(tetracycline = oxytetracycline < rolitetracycline < demeclocycline<chlortetracycline<doxycycline). The biological half-times (in hours) are as follows: chlortetracycline 6, tetracycline 8.5, oxytetracycline 10, demethylchlortetracycline 12, and doxycycline 15. These compounds penetrate into the placenta. The concentration in the cerebrospinal fluid is lower than in the plasma. Tetracycline itself is an exception in that it achieves relatively high levels in the cerebraspinal fluid. These drugs are excreted in the bile, feces, and urine in bacteriostatic concentrations.

Side Effects

Tetracyclines irritate the mucous membrane of the gastrointestinal tract. In addition, they inhibit the enzymes of the intestine and pancreas, and also exert a detrimental influence upon the intestinal flora as the result of their bacteriostatic activity. Various gastrointestinal disturbances are the result. Since the normal flora of the mouth and vagina are also affected, just as in the intestine, pathogenic bacteria, fungi, and yeasts can invade whereas they normally would be inhibited by the presence of the resident bacteria. Therefore, occasionally rare infections occur which become septic and lead to death in a patient in poor general condition.

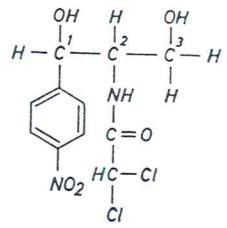
Photosensitization occurs following tetracyclines, apparently more often with demeclocycline. Patients should be protected from the sun. Liver damage has been observed in man only following high doses injected intravenously. Allergic reactions occur, but are rare. Tetracyclines are stored in the skeleton, especially the growing or fetal skeleton, and there produce disturbances in growth probably as a result of chelate formation with calcium. Growing teeth are likewise damaged and are discolored yellow or brown as the result of tetracycline storage. Therefore these antibiotics should be given to small children or following the fourth month of pregnancy only when absolutely necessary.

Indications and Use

Tetracyclines are called for in all infections which are caused by the organisms named above insofar as these cannot be inhibited by penicillin. Compounds of this group are administered usually in daily doses of 15–30 mg/kg by mouth. The dose of demeclocycline is smaller. The interval between single doses is determined by the rate of excretion. Rolitetracycline (*N*-[pyrrolidinomethyl]tetracycline) in the same dosage is suitable for parenteral (intramuscular, intravenous) administration when the drug is not tolerated by the oral route or in severe infections. Mild circulatory effects rarely occur after intravenous injection, although cases of severe anaphylactic shock have also been reported.

Chloramphenicol

Chloramphenicol, an antibiotic with bacteriostatic properties originally isolated from *Streptomyces venezuelae* and now prepared synthetically, has with slight exception the same spectrum of activity as the tetracyclines. Chloramphenicol inhibits protein synthesis by suppressing the transfer of activated amino acids. The compound is rapidly absorbed after oral administration. The blood level reaches a maximum within 2 hr. Because of its rapid excretion by the kidney, chloramphenicol has disappeared from the blood within 8 hr. The drug distributes itself uniformly throughout the body, penetrates well into the cerebrospinal fluid and pleural spaces, and passes the placenta.



Chloramphenicol
D(−)-Threo-2-dichloroacetamido-1-p-nitrophenyl-1,3-propanediol

Side Effects

Following longer term administration (10 days and more), occasionally even earlier, severe toxic damage to the hematopoietic system can occur under certain

circumstances, including agranulocytosis, thrombopenic purpura, or aplastic anemia, all of which are frequently reversible. One should distinguish this type of damage from a second, more rarely occurring, although usually lethal, form of bone marrow damage with aplasia and pancytopenia. This condition is not dose dependent and frequently occurs weeks or months after the last dose. Chloramphenicol inhibits microsomally regulated protein synthesis of warm-blooded animals. This phenomenon explains why the biotransformation of such drugs as tolbutamide, diphenylhydantoin, and dicoumarol may also be retarded. In premature infants and those less than a month old, the so-called "gray-baby" syndrome may occur after injudicious dosing (resulting in bloated abdomen, pale cyanosis, and peripheral circulatory collapse), sometimes leading to death (cf. p. 333). With typhoid fever, therapy must be initiated with small doses. Otherwise, the danger of the Herxheimer reaction is present; namely, the body is overwhelmed with free endotoxins as the result of rapid destruction of the bacteria. Very severe, possibly lethal, circulatory shock can be produced.

Indications and Use

The indications for chloramphenicol should be restricted to diseases that cannot be treated successfully with other drugs. These are, for instance, the case in *H. influenza* meningitis and in many conditions of pyelonephritis that are otherwise resistant to therapy. Until recently, major application was in typhoid fever, but also in this infection it is possible to utilize, at least initially, other drugs (e.g., ampicillin and the combination of trimethoprim and sulfonamide). The daily dose, which must be divided initially into six and later four single doses, is of the order of 30–40 mg/kg orally; in typhoid 10 mg/kg on the first day. Chloramphenicol also can be given parenterally or rectally in suitable preparations.

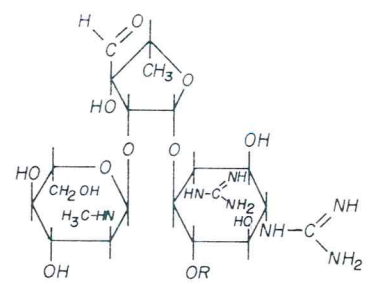
Aminoglycosides

The following antibiotics are termed aminoglycosides because of their chemical relationship: streptomycin, neomycin, kanamycin, paromomycin, gentamicin. They are also very similar with regard to the following pharmacological properties: disturbance of protein synthesis in bacteria, antibacterial spectrum, poor intestinal absorption, and toxic side effects. All aminoglycosides induce damage in the eighth cranial nerve and in this regard show additive effects. The sites of damage are the sensory cells of the cochlea and the labyrinth.

Streptomycin

Streptomycin is an antibiotic from *Streptomyces griseus*, an actinomycete. Chemically it is a base, which is usually available as the sulfate.

On the basis of its good tuberculostatic activity, streptomycin is still today one of the most important tuberculostatic agents. As is true of other microorganisms, with this drug the development of streptomycin-resistant tubercle bacilli can take place especially with the use of large doses. For this reason, one must attempt to use



Streptomycin

doses as low as possible. This is accomplished by combination therapy with at least one other tuberculostatic agent.

For all practical purposes, streptomycin is not absorbed from the gastrointestinal tract. Following the usual intramuscular injection, 30–60% of the compound is excreted within 12 hr by the kidney; the remainder, insofar as it is not metabolized, in the following 12 hr. Its excretion is retarded in cases of impaired renal function.

Streptomycin is distributed in the extracellular space. It penetrates into the cerebrospinal fluid only in the presence of an existing meningitis; it is not detectable in normal cerebrospinal fluid. It does enter the aqueous humor of the eye and peritoneal fluids. Fetal blood contains one half the concentration found in the maternal blood.

Side Effects

Streptomycin is a local irritant. This should be considered when giving injections and particularly with intrathecal administration. In addition, allergies are possible following streptomycin contact with the skin, even in nursing personnel. The most generally feared side effect is damage to the eighth cranial nerve which usually is first exhibited in disturbances in the vestibular portion and later or simultaneously to the acoustic portion. With daily doses of 1 gm of streptomycin, 10–20% of all cases will exhibit vestibular damage after 4 months; with 2 gm daily, 80%. With daily doses of 0.75 gm, the vestibular damage is noticeably reduced. Damage to the acoustic portion of the nerve can be expressed not only as deafness, but also as a disturbing roaring noise in the ear which can persist despite continued deafness.

Streptomycin is as toxic in normal doses in the presence of impaired renal function as it is with an overdose in cases of normal renal function. It is better to give smaller doses more frequently than intermittent large doses. All cranial nerve damage is irreversible and it may continue to worsen for some time following discontinuance of the medication. The vestibular damage is largely compensated with the help of the eye and compensatory reflexes; such is not the case for the hearing loss. Repeated tests of ear function are therefore necessary during streptomycin therapy. Such a test prior to the initiation of therapy is desirable because

previously damaged ears are more sensitive than normal. Intrauterine damage to the eighth nerve must be expected. Contrary to continued statements, pantothenic acid does not diminish the toxic effects of streptomycin upon equilibrium and hearing.

Indications and Use

Streptomycin should be used only against tuberculosis because of the resistance of most strains of bacteria and the risks associated with the side effects. In the treatment of this disease, it still remains an indispensible agent, especially in serious cases. Since the drug is practically always given in combination with other tuberculostatics, daily doses of streptomycin of 0.5–1 gm intramuscularly and distributed between two to three single doses are sufficient. In severe cases, daily doses of 1–1.5 gm are necessary and occasionally even higher doses in cases of tubercular meningitis, miliary tuberculosis, or following surgical treatment of pulmonary tuberculosis. Streptomycin can also be given by prolonged intravenous infusion.

Dihydrostreptomycin

Dihydrostreptomycin has the same spectrum of antibacterial activity as streptomycin. Microorganisms resistant to streptomycin are also resistant to dihydrostreptomycin (cross resistance). The compound was used for some time because it elicited somewhat less severe vestibular damage. However, since the acoustical damage for which there is no compensation occurs more easily than after streptomycin, dihydrostreptomycin should no longer be used, not even in combination preparations.

Neomycin

This antibiotic from *Streptomyces fradiae* inhibits numerous gram-positive and gram-negative bacteria. It is extraordinarily resistant to destruction by heat and digestive enzymes, and has a long shelf life. Neomycin sulfate is used mostly for topical application in infectious skin diseases such as pyogenic or secondary dermatoses, ulcerations, secondary burn infections, conjunctivitis, etc. Since neomycin is not absorbed from the gastrointestinal tract, it inhibits bacterial growth in the intestine after oral administration. In this way the intestine can be largely freed of its bacterial population prior to surgery with total doses of about 9 gm orally over 24 hr. The consequent infectious complications which can develop from the growth of unusual organisms can result in serious illness. On the other hand, the formation of ammonia can be markedly depressed by inhibition of the growth of intestinal bacteria in cases of hepatic coma, so that the tolerance to protein is noticeably increased. Neomycin should be given intramuscularly only in life-threatening situations, such as massive infections by *Proteus* or *Pseudomonas*. In such cases damage to the eighth nerve and the kidneys as well as a certain curarelike effect should be expected. The latter is also observed after polymixin therapy.

Paromomycin

This antibiotic obtained from *Streptomyces rimosus* has indications similar to those of neomycin. In addition to its activity in bacterial infections of the intestine, it also has amebicidal properties.

Kanamycin

Kanamycin is prepared from strains of *Streptomyces kanamyceticus*. It is a polybasic compound consisting of two amino sugars with glycoside links to deoxystreptamine. Its antibacterial activity *in vitro* is almost completely identical to that of neomycin. It is also effective against most staphylococci and the tubercle bacilli. Kanamycin is inactive toward streptococci, pneumococci, and Clostridium. Unfortunately, resistance to kanamycin develops within a short time. No cross resistance exists with penicillin and broad-spectrum antibiotics; cross resistance does develop to neomycin. Kanamycin passes the blood–brain barrier only in cases of meningitis. To maintain a sufficient blood level, intramuscular injections must be repeated in 8–12-hr intervals.

Side Effects

Depending upon the magnitude of the dose and the duration of treatment, kanamycin can elicit irreversible damage to the cochlear nerve in every patient. Repeated testing of acoustic function is necessary, although deafness, humming in the ears, and dizziness may occur even after the drug has been discontinued. The ototoxic effects of kanamycin, streptomycin, and neomycin are additive. Nephrotoxic effects that may be occasionally noted appear to be fully reversible in patients without previous kidney damage. Some painful local irritation may be noted upon intramuscular injection; allergic reactions are seldom observed.

Indications

Because of the ototoxicity, it is necessary to judge very carefully the indications for its use in every case and to attempt to use the lowest doses possible for the shortest periods of time. Daily doses of 15 mg/kg should not be exceeded; even smaller doses are called for in the presence of kidney disease.

Gentamicin

This compound, of all the aminoglycosides, possesses the widest spectrum of activity and therefore can be used against strains which are resistant to neomycin or kanamycin. As with the other representatives of this group, this antibiotic can damage equilibrium, hearing, and kidneys. It is given for infections with *Pseudomonas aeruginosa*, *E. coli*, strains of *Proteus*, *Klebsiella*, and staphylococcus, particularly when the infection occurs in the urinary tract or is superimposed upon burns (also with local application).

Erythromycin, Macrolides

Antibiotics of this group possess a macrocyclic lactone ring structure, a macrolide. Erythromycin, an antibiotic obtained from *Streptomyces erythreus*, has a spectrum of activity between that of penicillin and the tetracyclines. The compound should be utilized above all in cases of penicillin allergy and for the treatment of infections with penicillin or tetracycline-resistant staphylococci and enterococci. However, erythromycin-resistant staphylococci can also develop. In the usual doses erythromycin is bacteriostatic. Since it is destroyed by acid, it must be administered in capsules which are not soluble in the gastric juice. It is generally given in doses of 0.3–0.4 gm orally at intervals of 6 hr. Side effects involving the gastrointestinal tract can occur (nausea, vomiting, and diarrhea). Following administration of the acid-stable, and therefore more potent, water-soluble erythromycin estolate, cholestatic hepatitis has occasionally been observed which probably is the result of the development of hypersensitivity. Such a side effect has not been described following oral administration of the stearate salt or after the ethyl succinate or lactobionate derivatives for intramuscular or intravenous injection.

Oleandomycin and spiramycin are other antibiotics derived from strains of *Streptomyces*. They have virtually the same spectrum of activity as erythromycin. Since all three compounds exhibit cross resistance with one another and have the same side effects, the indications and limitations for their use are the same.

Lincomycin

Lincomycin shows a spectrum of activity similar to that of erythromycin, but is not a macrolide. Since it is rather markedly accumulated in bone, lincomycin is particularly recommended in osteomyelitis.

Polypeptides

Bacitracin

Bacitracin is a mixture of bacteriocidal polypeptides obtained from *Bacillus subtilis* which is active against numerous gram-positive organisms such as staphylococci, streptococci, pneumococci, anaerobic cocci, clostridia, as well as spirochetes, amebas, gonococci, and meningococci. It is inactive against most aerobic gram-negative bacteria. Like penicillin bacitracin inhibits the formation of the bacterial cell wall. The drug often has effects on infections which do not respond to penicillin. Bacitracin in neither absorbed from the gastrointestinal tract nor from the meningeal spaces following local application. It is frequently combined with neomycin for the local treatment of infections of the skin and mucous membranes. Because of its nephrotoxicity, it should be used only for the treatment of systemic infections in life-threatening situations in which other agents have failed. In such cases bacitracin is injected intramuscularly in three divided doses with a daily dose of 100,000 IU at the most. The oral daily dose is also about

100,000 IU; for external use salves and solutions with about 500 IU per gram are used.

Polymyxin B

Some bacteriocidal polymyxins have been obtained from the spore-forming soil bacterium *Bacillus polymyxa*; of these polymyxin B is the least toxic. It is a basic polypeptide with a molecular weight of about 1000. It increases the bacterial cell wall permeability such that low molecular weight compounds are lost. Polymyxin is active only against gram-negative bacteria, especially *Pseudomonas aeruginosa*, *Aerobacter aerogens*, *Escherichia coli*, the *Shigella* group, and *Haemophilus influenza*. The development of resistant strains does not appear to occur. In systemic infections, polymyxin B must be injected in divided doses as the sulfate intramuscularly every 6–8 hr and not more than 2.5–3 mg/kg daily. Intrathecal administration is indicated in cases of meningitis. Absorption from the gastrointestinal tract cannot be expected. Doses for oral administration are 75–100 mg, four times daily. The compound has neurotoxic and nephrotoxic side effects. Paresthesia, vertigo, dizziness, and fever occur. Kidney function must be tested, especially if previous kidney damage exists.

Polymyxin E (colistin) is a cyclic peptide with bacteriocidal properties obtained from the spore-forming *Bacillus colistinus*. The antibacterial effects and the side effects coincide to a large extent with those of polymyxin B.

Tyrothricin

Tyrothricin is obtained from the spore-forming soil bacterium *Bacillus brevis*. It consists of two polypeptides, gramicidin and tyrocidine. Its activity extends to gram-positive microorganisms and fungi. The compound is used only for local applications to wounds, or for the irrigation of body cavities, or for inhalation; it is not suitable for oral or parenteral administration. Lavage in the neighborhood of the subarachnoid space should be avoided because of the danger of irritation to the meninges. The effective concentration of tyrothricin for local application is about 0.25–0.5 mg/ml.

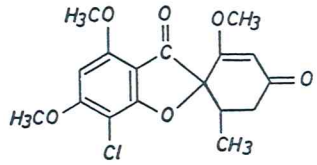
Antibiotics with Antifungal Activity

Nystatin is an antibiotic from *Streptomyces noursei* that can be successfully utilized for the local treatment of *Candida albicans* infections of the mouth and vagina. With sufficient dosage it is also suitable for the treatment and prophylaxis of intestinal infections. The dose is 500,000 U by mouth every 8 hr.

Amphotericin B is an antibiotic from strains of *Streptomyces nodosus* which possesses fungistatic rather than fungicidal activity against various systemic fungal diseases. It should be considered in cases of histoplasmosis, blastomycosis, some infections with *Cryptococcus neoformans* (*Torula histolytica*), other fungi, and sometimes *Candida*. Amphotericin B must be administered intravenously with a prolonged infusion since it is not effective following oral administration. Because

of its marked local irritant properties, it must be used in high dilution for intravenous infusion as well as for injection into the cerebrospinal fluid in cases of meningitis. Daily doses are 0.25–1 mg/kg. Therapy must be continued for at least 4–8 weeks. Side effects occur in the form of various allergic reactions. Abdominal pain, diarrhea, and loss of appetite occur. Damage to renal function must be expected and the blood levels of urea and nonprotein nitrogen are elevated.

Griseofulvin is an antibiotic from penicillin mold that following oral administration is accumulated into skin, hair, and nails and acts as a fungistatic agent at these sites. Various infections can thus be treated, including microsporosis, trichophytosis, and epidermophytosis. Therapy must be carried on for weeks, and if the



Griseofulvin

nails are involved, for months. This is necessary because griseofulvin is only incorporated into newly formed keratin and protects it from fungal attack. The otherwise usual local treatment should not be neglected. Griseofulvin is inactive against *Candida albicans*, *Pityriasis versicolor*, erythrasma, actinomycetes, and bacteria. Daily doses of 0.5–1 gm distributed over two to four single doses are generally sufficient; with severe infections the dose may have to be transiently increased to 2 gm. Gastrointestinal disturbances occur, as well as various allergic skin reactions and a syndrome similar to serum sickness. Leukopenia and damaged liver function, which have been observed on occasion, have always been reversible. Occasional headache disappears after several weeks in spite of continued treatment. Some cases of mental confusion have been observed after daily doses of 2 gm. On the other hand, the same dose has no effect on spermatogenesis even after 3–6 months, although like colchicine, the compound inhibits cell division at metaphase. Thirty to 50% of all patients exhibit fragmented hemorrhages under the nails.

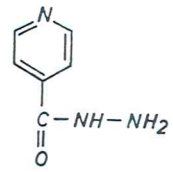
Tuberculostatic Agents

A number of drugs is available for the treatment of tuberculosis. In principle with this disease at least two tuberculostatic agents should be combined. As first choice isoniazid, rifampin, *p*-aminosalicylic acid (PAS), ethambutol, and streptomycin should be taken into consideration. At present, the combination of isoniazid with ethambutol is considered to be the most suitable one. (Concerning combination preparations, see p. 269 and p. 331).

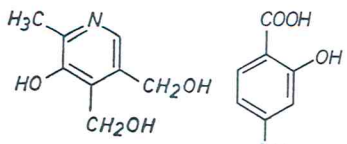
Isoniazid

Isoniazid is the most useful and versatile tuberculostatic agent. It has an inhibitory effect upon the tubercle bacilli *in vitro* in concentrations as low as 0.05

mg/liter while the corresponding concentration of streptomycin is about ten times greater and that of *p*-aminosalicylic acid even higher. The mechanism of action of isoniazid is unknown.

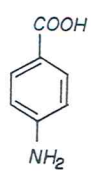


Isoniazid, INH
Isonicotinic acid hydrazide



Pyridoxine
Vitamin B_6

p-Aminosalicylic acid (PAS)



p-Aminobenzoic acid

Isoniazid is absorbed well and rapidly from the gastrointestinal tract. Maximum blood levels are achieved within 1–3 hr. After a dose of 3 mg/kg by mouth, a tuberculostatic blood level of at least 0.4 mg/liter can be detected for an additional 6–24 hr. The compound distributes itself evenly throughout the body; it penetrates into the placenta and all body fluids, including the cerebrospinal fluid. This is of prime importance in the treatment and prophylaxis of tubercular meningitis. The changes in blood level with time following intramuscular injection are similar to those following oral administration. While approximately 10% is excreted unchanged in the urine, the largest fraction appears in the urine as the acetylated derivative which does not possess bacteriostatic activity (cf. also p. 332).

Side effects are primarily observed on the central nervous system with the necessarily long-term course of treatment with isoniazid. This may lead to dizziness, headaches, numbness, hyperreflexia, muscle twitching, paresthesia, and very seldom, encephalopathy. Dryness of the mouth and gastrointestinal and urinary disturbances also occur. Occasionally, liver damage and agranulocytosis have been reported. The peripheral nervous system disturbances with the usual doses can be improved by the simultaneous administration of pyridoxine without reducing the chemotherapeutic effect. It appears as if the central nervous system side effects may be favorably influenced by glutamic acid.

The use of isoniazid is restricted to the treatment and prophylaxis of tuberculosis. In order to avoid the more marked side effects and to prevent the development of resistant strains, combination therapy and the lowest possible dose should be undertaken, for instance, 4–5 mg/kg per day orally or if necessary such doses intramuscularly, distributed over three single doses. Only in cases of tubercular meningitis and miliary tuberculosis are the doses transiently doubled. It has been shown that clinical improvement can occur despite the development of resistant strains, probably because the virulence of the organism has decreased. Isoniazid chemoprophylaxis in tuberculin-negative children exposed to active cases of tuberculosis or for preventive chemotherapy in tuberculin-positive children following measles or whooping cough is continually increasing in importance. It is also used to prevent relapses in children and adults.

p-Aminosalicylic Acid

p-Aminosalicylic acid (PAS) inhibits the growth of tubercule bacilli in concentrations of 1 mg/liter. This inhibition can be abolished by the addition of the bacterial growth promoter, *p*-aminobenzoic acid, thereby exhibiting the competitive interaction of these two compounds.

p-Aminosalicylic acid is rapidly absorbed after oral administration. The blood level reaches a maximum after 1–2 hr, but then falls continually due to the rapid excretion by the kidneys. For this reason, large amounts of the compound must be administered in individual doses at intervals of 4–6 hr. The daily dose is usually 10–15 gm.

Side Effects

Various disturbances in the gastrointestinal tract must be expected because of the local irritant effect of *p*-aminosalicylic acid. Upper abdominal pain, loss of appetite, nausea, vomiting, and diarrhea can occur. The diminished prothrombin level in the blood, as with other salicylates, can be alleviated or prevented by administration of vitamin K. Inhibition of thyroxine production, a rare phenomenon caused by inhibition of iodine incorporation into the thyroxine molecule (an effect similar to that of methylthiouracil), can be counteracted by the administration of thyroid hormone. Various degrees of allergic reaction must be expected following *p*-aminosalicylic acid.

Indications and Uses

p-Aminosalicylic acid has a weaker tuberculostatic effect than streptomycin or isoniazid. However, it can be used very successfully in combination with the other tuberculostatic drugs, since the doses of the individual compounds can be lowered. At the same time, the danger of developing resistance is reduced.

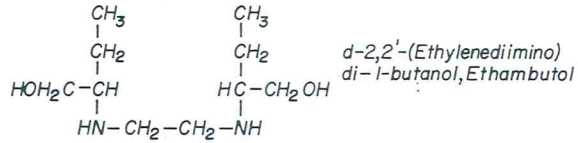
Rifampin

Rifampin belongs to the class of rifamycins, complex macrocyclic antibiotics from *Streptomyces mediterranei*. It is used only in the treatment of tuberculosis. Its mechanism of action is not known in detail. It impairs the bacterial RNA synthesis by affecting the DNA-dependent RNA polymerase. Similar effects in warm-blooded animals have not been excluded, since the drug is teratogenic in animals. For this reason rifampin should not be given during the first trimester of pregnancy. Before treatment is started the existence of pregnancy must be excluded.

Rifampin shows good activity with oral administration. It is uniformly distributed in the body, including the cerebrospinal fluid. The highest concentrations are found in liver and bile. The daily doses are in the range of 450–600 mg, given daily as a single dose combined with other tuberculostatic agents. Rifampin is contraindicated in cases of liver damage. Gastrointestinal disturbances and allergic reactions may occur.

Ethambutol

Ethambutol is well absorbed and mainly excreted via the kidneys. The mechanism of action is unknown. It is only suitable for combined therapy. Ethambutol is successfully used as a tuberculostatic, especially if resistance to other drugs has developed. Side effects are relatively rare. Leukopenia, allergic reactions, peripheral neuritis, and renal damage may occur. An impairment of visual acuity and the loss of the ability to see green colors have been reported. The disturbances of vision are reversible if treatment is interrupted in an early stage. If therapy is still continued, the danger of retrobulbar neuritis exists. Renal damage is a relative contraindication. The normal daily dose amounts to 15–25 mg/kg, given once daily.



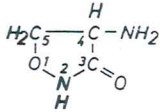
d-2,2'-(Ethylenediimino)
di-1-butanol, Ethambutol

Viomycin

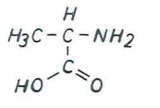
This strongly basic polypeptide obtained from *Streptomyces puniceus* is active against tubercle bacilli regardless of whether they exhibit sensitivity or resistance toward streptomycin and isoniazid. Development of resistance to viomycin must be expected. For this reason and above all because of its dangerous side effects, it should only be given in low doses and in combination with another tuberculostatic agent. Since viomycin is insufficiently absorbed upon oral administration, it must be given intramuscularly. Doses of 2 gm (1 gm 12 hr apart) are given every third day. The side effects can be important. Severe damage to renal function and electrolyte imbalance, as well as damage to the eighth cranial nerve can occur. The usefulness of viomycin is considerably reduced by such toxicity.

Cycloserine

Cycloserine, which is derived from strains of *Streptomyces*, is ineffective against a number of bacteria, but in exceptional cases should be considered for the treatment of tuberculosis. The tuberculostatic activity is less than that of the other agents. Cycloserine interferes with the utilization of amino acids, especially alanine to which it is related chemically, in the formation of the bacterial cell wall. The toxic side effects are considerable and can occur even in therapeutic doses. Head-



D-Cycloserine
D-4-Amino-3-isoxazolidinone



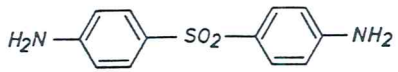
D-Alanine

ache, dizziness, and apathetic or psychotic conditions occur, as well as petit mal or grand mal convulsions. All of these effects are reversible when the drug is with-

drawn. With two oral daily doses of 250 mg the toxic reactions are less to be feared. With such a dose the blood levels will be 25–30 mg/liter.

Agents Used against Leprosy

Certain sulfones prepared in the course of sulfonamide synthesis exhibited tuberculostatic activity which was, however, insufficient for therapeutic purposes. On the other hand, compounds from this group have proved to be useful for the treatment of leprosy; for instance, 4,4′-diaminodiphenylsulfone (dapsone) and its derivative glucosulfone, which can be administered intravenously. The mechanism of action of these compounds is not clear. As is the case with sulfonamides, a certain degree of antagonism can be demonstrated between the sulfones and *p*-aminobenzoic acid. Other sulfonamides are ineffective against leprosy. 4,4′-Diaminodiphenylsulfone has numerous side effects, some of which are very serious, such as hemolytic anemia, neuritides, psychoses, and liver damage.



Dapsone
4,4′- Sulfonyldianiline
(4,4′- diaminodiphenylsulfone)

Thiambutosine (4-butoxy-4′(dimethylamino)thiocarbanilide) is a useful drug but the organisms develop resistance to it after 2–3 years.

Some tuberculostatic agents have more or less marked activity against leprosy. Streptomycin cannot be used because of its ototoxic side effects. Isoniazid and *p*-aminosalicylic acid have insufficient activity. Thiacetazone, which has been surpassed by better drugs in tuberculosis, is sometimes effective in leprosy. The effect of rifampin seems to be comparable to that of 4,4′-diaminodiphenylsulfone.

Agents Used against *Trichomonas* Infection

Treatment of *Trichomonas* infection of the vagina is best managed with metronidazole (2-methyl-5-nitroimidazole-1-ethanol), given orally in daily doses of 0.5–0.75 gm for 5–10 days. The sexual partner of the infected patient should always be treated as well.

Antimalarial Agents

Since the malaria parasite during each phase of its existence in the human body not only has a different appearance, but apparently also a different metabolism, various drugs are necessary for the various phases. The sporozoites transmitted with the mosquito bite cannot be killed by any available drug. The primary exoerythrocytic forms occurring during the primary tissue phase are difficult to deal

with therapeutically and are affected by only a small number of compounds. The schizonts appearing during the asexual phase can be eradicated more easily but in most cases with drugs other than those effective against the gametes occurring during the sexual phase. Especially in infections with *Plasmodium vivax* and *Plasmodium malariae*, a chronic, secondary tissue phase may follow upon the primary tissue phase; it must be treated in the same way as the primary phase.

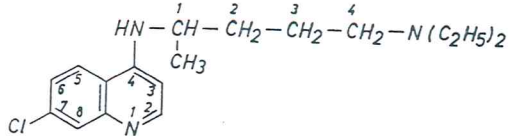
The classic antimalarial drug which was the sole agent in use for hundreds of years was the bark of the cinchona tree or the alkaloid, quinine, isolated from it. This compound is capable in many cases of preventing the acute symptoms originating with the schizonts, but it usually cannot prevent relapses. In some tropical areas one has been forced to rely again upon quinine since the malaria-causing organisms have developed complete resistance to the modern antimalarial drugs. For a radical cure of malaria, the drug or a combination of several agents must eradicate blood schizonts, gametes, and exoerythrocytic tissue forms (tissue schizonts). Therapy which suppresses only transiently the clinical symptoms or which is for prophylaxis (sometimes of practical use), is designated as suppressive treatment. Such therapy must later be concluded with a radical cure. Since in infections by *Plasmodium falciparum*, all exoerythrocytic forms enter into the blood, it is sufficient in this disease to administer an agent active against the schizonts at the proper time.

True prophylaxis against malaria by means of drugs is not yet possible. Such drugs would have to kill the sporozoites or other preerythrocytic forms.

The best chemotherapeutic agents effective against the various forms of malaria are chloroquine, primaquine, and pyrimethamine. In cases of resistance developed to modern drugs, recourse to quinine is possible.

Chloroquine

Chloroquine is a drug highly active against the blood schizonts of all forms of malaria. Chloroquine effects a complete cure of infections with *Plasmodium falciparum* in addition to abolishing the acute attacks. On the other hand, in a *Plasmodium vivax* or *P. malariae* infection only the acute symptoms caused by the schizonts are counteracted or prevented by suppressive therapy. In all such cases subsequent or simultaneous treatment with primaquine should be undertaken for the eradication of the gametes and the extraerythrocytic forms. Even in falciparum malaria, the elimination of the gametes (which are usually present for only a brief time) by administration of primaquine is worthwhile in order to prevent their transmission to the *Anopheles* mosquito.



Chloroquine
7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline

Chloroquine is rapidly absorbed from the gastrointestinal tract. The liver may contain concentrations of chloroquine 500 times higher than that of the plasma. This strong binding to various tissues is responsible for the drug's long duration of action. It is also of importance in the therapy of ameba infections of the liver (cf. p. 297). Oral doses of 2.5 gm of chloroquine diphosphate (corresponding to 1.5 gm of free base), distributed over 2–3 days are usually sufficient for the treatment of a malarial attack. Intramuscular injections are only rarely necessary. A dose of 0.5 gm is given every 7 days for suppressive therapy.

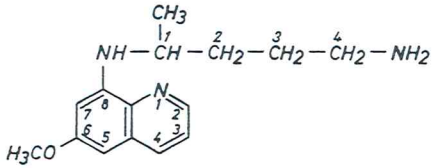
Side Effects

In suppressive therapy of malaria, headache, itching, visual and gastrointestinal disturbances are sometimes observed. All are reversible following withdrawal of the drug. Numerous other side effects occur with long-term therapy for lupus erythematosis and chronic rheumatic arthritis. These are discussed on page 145.

Primaquine

Primaquine has completely replaced the related compound, pamaquine, because of its less severe side effects.

Primaquine has good activity against the extraerythrocytic forms of malaria and against all gametocytes, while it does not completely eliminate blood schizonts. For this reason, combination therapy with chloroquine is necessary. Primaquine is rapidly absorbed from the gastrointestinal tract and is largely metabolized in the body. The remainder is excreted within a short period of time. The compound is not stored in the body. The side effects of primaquine are, in general, slight. Occasionally, there is loss of appetite, nausea, abdominal pain, some slight methemoglobin formation and rarely granulocytopenia. Worthy of note is a primaquine idiosyncratic reaction resulting from genetically determined biochemical deficiency. Primaquine elicits intravascular hemolysis in these patients (for further discussion cf. p. 333).



Primaquine
8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline

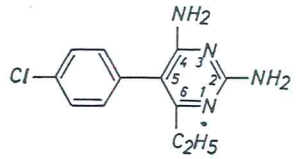
Indications

Primaquine is suitable for eliminating the exoerythrocytic forms and the gametocytes after treatment of the acute malarial symptoms with chloroquine. It is given in doses of 15 mg by mouth for 14–15 days. The same schedule of treatment

should be used if a malaria infection is suspected following the patient's leaving an infectious area. A course of 3 days' treatment is sufficient to eradicate gametocytes.

Pyrimethamine

Pyrimethamine is a further development of compounds which have antimalarial activity such as the biguanide derivative, chlorguanide, and on the other hand, pyrimidine derivatives with antifolic acid activity. It exhibits good activity against exoerythrocytic forms, but the effect on schizonts producing acute symptoms occurs too slowly. Disease transmission is interrupted since the drug inhibits the sporogonia in the mosquito.



Pyrimethamine
2,4-Diamino-5-(p-chlorophenyl)-6-ethylpyrimidine

The compound is slowly but completely absorbed from the gastrointestinal tract. It persists for some time in the body. A weekly oral dose of 25 mg is sufficient for suppressive therapy. Pyrimethamine should be combined with chloroquine in cases with acute symptoms. Strains resistant to chlorguanide are also resistant to pyrimethamine. Megaloblastic anemia can occur only after large doses, and regresses following withdrawal of the drug. This side effect is the result of the antifolic acid activity of pyrimethamine and has sometimes been used for the treatment of polycythemia. A more rapid action against *Plasmodium vivax* is displayed by methotrexate, a folic acid antagonist related to pyrimethamine (cf. p. 306).

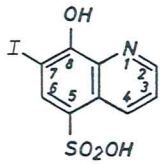
Chemotherapy of Amebiasis

In the treatment of infections with *Entamoeba histolytica*, drugs active against the vegetative trophozoites must be differentiated from those active against the cysts. Emetine and the antimalarial drug chloroquine are very effective against the trophozoites which cause the acute symptoms in the intestine and in liver (hepatitis, liver abscess). Chloroquine is to be preferred because of its lesser side effects. Chloroquine is given orally in doses of 250 mg, four times daily during the first 2–4 days and then twice daily for 10–14 days. To avoid the establishment of a chronic infection, the eradication of trophozoites by emetine or chloroquine must be accompanied by treatment of the intestinal forms with the drugs mentioned below. The intestinal forms are best treated by the administration of halogenated quinoline derivatives, or organic arsenicals, or a combination of tetracycline with these drugs.

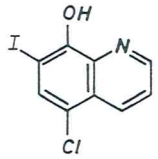
Emetine is an alkaloid obtained from the dried root of *Cephaelis ipecacuanha*. This root has been used against dysentery for centuries, while the pure compound has been used with success for several decades against the trophozoites. However, because of its toxic side effects on the heart, the vasculature, the nervous system, and the intestinal tract, this drug should be avoided when possible.

Halogenated Quinolines

Some iodinated quinolines are useful against the intestinal forms of amebic dysentery, for instance, chiniofon, which has been used for more than 40 years, or the related compound iodochlorhydroxyquin. In addition, these agents are disinfectants. They possibly act by liberating free iodine. Absorption from the intestine is slight. However, because of their slow excretion one must consider the



Chiniofon
8-Hydroxy-7-iodo-5-quinolinesulfonic acid



Iodochlorhydroxyquin
5-Chloro-7-iodo-8-quinolinol

possibility of accumulation. Nausea, diarrhea, and headaches can occur. In amebic dysentery, chiniofon is given orally in doses of 0.5 gm three times a day for 1 or 2 weeks; iodochlorhydroxyquin, 250–500 mg, three times a day for a period of 1 or 2 weeks. Enemas containing high doses are not necessary if combined therapy with chloroquine is utilized. (For side effects see p. 260.)

Organic Arsenicals

Organic compounds containing pentavalent arsenic have been given in the treatment of amebic dysentery with uncertain success for a long time. Their only effect is upon the intestinal infection. The toxicity of glycobiarsol [oxo(hydrogen *N*-glycoloylarsanilato)bismuth] is low because of poor solubility and intestinal absorption. The drug should be combined with chloroquine in extraintestinal infections and deeply seated ulcerative processes. The drug should not be given in cases of arsenic hypersensitivity and preexistent liver and renal damage. The dose is 0.5 gm three times daily for 7 days by mouth.

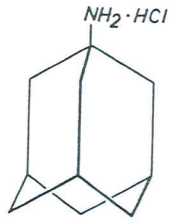
Tetracyclines are frequently active against the intestinal forms of amebic infections, as is bacitracin. These drugs, the other actions of which have already been considered, are given either alone or in combination with other agents. A combination of glycobiarsol with chloroquine is necessary for extraintestinal forms. Oxytetracycline or chlortetracycline is given orally for 10 days in doses of 0.5 gm every 6 hr.

Agents Used against Other Tropical Diseases

In conditions of lambliasis the acridine derivatives that were previously used against malarial schizonts (e.g., quinacrine) have proved to be useful. In trypanosomal diseases, especially African sleeping sickness, suramin is active for 3 months as a prophylactic and in early stages that are not yet plasma positive. Later stages of the disease can be treated with tryparsamide (*N*-[carbamoylmethyl]-arsanilic acid). Suramin is also effective against the adult forms of filarial worm, *Onchocerca volvulus* and sometimes pemphigus, lichen ruber planus, and mycosis fungoides. In leishmaniasis and schistosomiasis, various antimony compounds may be used, i.e., antimony potassium tartrate (tartar emetic) and stibophen (sodium antimony bis[pyrocatechol-2,4-disulfonate]). Lucanthone (1-[(2-diethylaminoethyl)-amino]-4-methylthioxanthen-9-one hydrochloride) is effective against *Schistosoma haematobium*. A therapeutic agent in filariasis is diethylcarbamazine (*N*,*N*-diethyl-4-methyl-1-piperazinecarboxamide).

Antiviral Agents

Currently, the combat against viral infections consists of active immunization or the administration of gamma globulin. In spite of certain therapeutic successes with some viral diseases, the specific chemotherapy of these infections is still in the early stages of development. However, a favorable development appears to have occurred in the prophylaxis of variola. Methisazone (1-methylindole-2,3-dione 3-thiosemicarbazone) has been found to be very effective in a large experimental series on humans, if it is given during the incubation period. It frequently causes vomiting. Idoxuridine (2′-deoxy-5-iodouridine) is an iodinated analog of thymidine.



Amantadine
1-Adamantanamine

It blocks the utilization of thymidine by the virus; it acts as an antimetabolite of nucleic acid synthesis. Idoxuridine is active following local application only in cases of herpes simplex keratitis. It is hardly active at all in cases of keratitis disciformis and inactive in herpes infections of the skin. Development of resistance is frequently observed.

Experiments were undertaken with amantadine (*l*-adamantanamine hydrochloride) to therapeutically affect influenza virus with virostatic agents. It reduces

the number of cases of illness from influenza type A_2 by approximately 50% when taken at least 24 hr prior to exposure. The compound is ineffective against other types of influenza. It is not viricidal but inhibits the penetration of the virus into the host cells. In the course of treatment with amantadine, disorders of the gastrointestinal tract, mild central nervous disturbances, and hallucinations may occur. The daily dose of 100 mg should not be exceeded in influenza prophylaxis. The second field of application of amantadine, Parkinsonism (cf. p. 130) usually requires higher doses. The frequency and intensity of the side effects correspondingly increase. Daily doses of 200 mg should not be exceeded.

CHAPTER 8

CHEMOTHERAPY OF NEOPLASTIC DISEASES

Cytostatic Agents

Cytostatic agents inhibit the development and replication of rapidly growing cells. Therefore they are used to inhibit tumor growth and the progression of neoplastic diseases of the hematopoietic system. However, their effect is not so specific that other tissues with rapid cell division are not affected as well. Therefore, with all agents of this group which have so far been used, even with therapeutic doses, inhibition of the functions of the bone marrow, the reproductive glands, the growth of hair, and the growth of the fetus, must be expected.

Apart from such nonspecific damage to cells, inhibition of cellular antibody formation by cytostatic agents is demonstrable. This effect is used to depress or suppress immune reactions as immunosuppressive therapy. Drugs from all classes of cytstatics are used for this purpose, i.e., cyclophosphamide, 6-mercaptopurine, azathioprine, methotrexate, actinomycin C. Analogous effects can be obtained with ionizing radiation. Glucocorticoids and antilymphocyte serum also exhibit immunosuppressive properties, although on the basis of other mechanisms of action. Their application to therapy is, with the exception of the latter, very limited because of the risk of side effects (embryonic and genetic changes, carcinogenesis).

We are still far removed from the selectivity of action that characterizes the chemotherapy of the diseases caused by microorganisms. Nevertheless, the neoplastic process can be suppressed to a considerable extent with careful use of a prudently chosen compound. Thus some cases of polycythemia, lymphogranulomatosis (Hodgkin's disease), leukemias, lymphosarcoma, and other reticuloses can

be so treated. On the other hand, carcinomas are not influenced or if at all only to a slight extent. An exception, as far as side effects are concerned, is found in the hormones of the adrenal cortex and the gonads which are used for the treatment of some types of tumors. Since such hormones are not generally cytostatic agents, the side effects discussed above are not exhibited.

General Indications for Use

Cytostatic drugs are indicated only if conventional treatment by surgery or irradiation is not possible. Whether the frequently used "relapse prophylaxis" following surgical removal of a primary tumor really prevents the formation of metastases is very questionable, especially since the viability of normal cells and the formation of antibodies are also reduced. If the immune process is capable of inhibiting the development of tumors, the prophylactic administration of cytostatic drugs would damage the natural resistance. All cytostatic drugs lose their therapeutic activity after long-term administration. Moreover, carcinogenic effects should be taken into account.

Radioactive Isotopes

Radioactive isotopes act in the organism owing to their β or γ-radiation, that is, their physical properties. Again, tissues with a high rate of cell division are the most severely affected. Basically, the action and side effects of radioisotopes are the same as those occurring with X-irradiation. However, in special cases, the isotopes can be used preferentially for localized irradiation, i.e., radioactive gold (^{198}Au) or radioactive cobalt (^{60}Co). Selective accumulation in the cells which are to be irradiated is possible with radioactive phosphorus (^{32}P) for bone marrow or iodine (^{131}I) for the thyroid gland. Tolerance limits for carcinogenic effects of radioactivity cannot be quantitatively established. They are lower than has been previously assumed.

Indications and Use of ^{32}P

Radioactive phosphorus is a β-emitter with a half-life of 14.3 days. It is administered intravenously or orally as the phosphate ion. Following parenteral administration, one-half of the administered material is eliminated from the body after 8 days (the biological half-life is 8 days). ^{32}P is taken up into all cells, and in particularly high quantities into cells which are rapidly dividing. It is in such cells that the β-radiation has its most marked effect. Bone marrow is affected to the largest extent, which explains the use of this isotope in polycythemia. An intravenous dose of 3–6 mCi is given, and, depending upon the effect, repeated after several months. Such therapy is unfortunately accompanied by the later development of leukemia in a significant fraction of treated cases. The effects of ^{32}P in the treatment of myeloid or lymphatic leukemia as well as lymphogranulomatosis are less favorable.

Indications and Use of ^{131}I

Radioactive iodine is a β- and γ-emitter with a physical half-life of 8 days. ^{131}I accumulated in the thyroid acts to destroy the epithelium with its soft β radiation. Compared to X-irradiation, the use of ^{131}I is always advantageous if it is indeed accumulated, since other tissues (e.g., skin) are then more or less protected. The doses of ^{131}I used in hyperthyroidism are 1–2 mCi per month (cf. p. 217). The development of hypothyroidism must be expected with excessive doses. Damage to the reproductive cells can occur just as with other radioisotopes. Since the ability to store iodine is diminished in thyroid tumor tissue, ^{131}I is poorly accumulated in thyroid tumors and metastases. Such accumulation can be increased by means of thyrotropic hormone. The necessary doses for thyroid tumors are considerably higher than those used in hyperthyroidism, i.e., 0.25 mCi per gram of estimated tumor tissue. ^{131}I is used in very small doses as a diagnostic agent for thyroid function. The hard γ-radiation which leaves the body can be localized and quantitatively measured by means of a scintillation counter (scintigram).

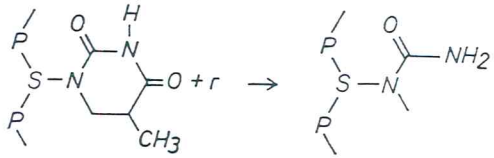


Fig. 59. The thymine residue of deoxyribonucleic acid is destroyed as the result of the interaction with a radical produced by radiation (P, phosphoric acid group; S, sugar).

Side Effects

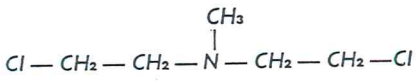
Following the administration of radioisotopes, basically the same tissue and functional damage can be expected as that caused by X-irradiation. The damage which is first to appear and most severe, is to the reproductive cells and blood cells, such as lymphocytes, myeloblasts, erythroblasts, leukocytes and thrombocytes. The epithelial cells of the intestinal mucosa are also damaged by radiation. In addition, one must consider the possibility that, as in animal experiments, mutations may occur that are expressed only after one or more generations. Procreation should be avoided for some months after the use of radioactive compounds. These compounds are contraindicated during pregnancy. The frequency of tumors and leukemia in children is increased following the use of radioactive compounds. The genetic damage inflicted by cytostatic agents and radiation is additive. Figure 59 shows an example of the change in a nucleic acid of the genetic material caused by radiation.

Alkylating Agents

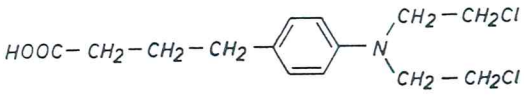
Compounds in this group have effects similar to those of radioisotopes. Therefore they have been called "radiomimetics." Here also cell

although not by radiation, but by chemical means. An example of such an alkylation is given in Fig. 60. In addition, such a mechanism explains the mutagenic and teratogenic effects as well as the development of tumors in experimental animals.

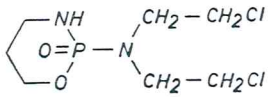
Mustard gas
Bis(2-chloroethyl)sulfide



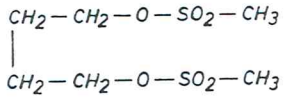
Nitrogen mustard
2,2'-Dichloro-N-methyldiethylamine



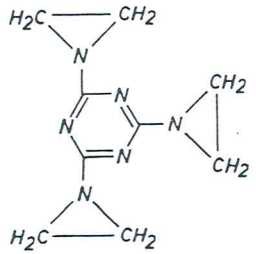
Chlorambucil
4-{p-[Bis(2-chloroethyl)amino]phenyl}
butyric acid



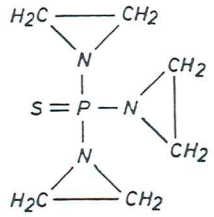
Cyclophosphamide
2-[Bis(2-chloroethyl)amino]tetrahydro-
2H-1,3,2-oxazaphosphorine 2-oxide



Busulfan
1,4-Butanediol dimethanesulfonate



Triethylenemelamine
2,4,6-tris(1-aziridinyl)-
s-triazine



Triethylenethiophosphoramide (thio-TEPA)
Tris(1-aziridinyl)phosphine
sulfide

On the other hand, they can prevent the growth of tumors under suitable conditions in a manner analogous to that of X-rays and radioactive isotopes in that these compounds transfer a labile alkyl residue to nucleic acids.

Nitrogen Mustard

Mustard gas, which was used as a chemical warfare agent during World War I, and the closely related compound, nitrogen mustard, exert apart from their marked, localized cell-damaging action, the effects described for alkylating agents. Mustard gas has never been used in chemotherapy.

Orally Active Alkylating Agents

A large number of compounds with basically the same activity and side effects as nitrogen mustard have been prepared. These newer compounds produce only slight local irritation of the gastrointestinal tract. Therefore, they can be given by mouth. Chlorambucil, triethylenemelamine, thio-TEPA, cyclophosphamide, and busulfan belong to this group. In part, these compounds are converted within the body into the active therapeutic agents; i.e., with cyclophosphamide, the cyclic P-NH bond is cleaved.

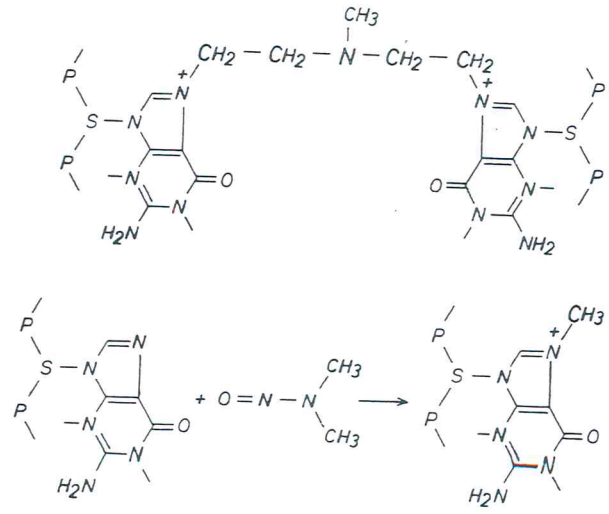


Fig. 60. Examples of the alkylation of nucleic acid units which are functionally affected by condensation or simple alkylation (formation of quaternary salts). Top: Reaction with nitrogen mustard. Bottom: Reaction of dimethylnitrosamine (P, phosphoric acid group; S, sugar). Two naturally occurring base pairs can be condensed by alkylation; also anomalous pairing can occur as pictured above.

Side Effects

The serious local cell damage experienced with nitrogen mustard rarely occurs with the oral agents of this group, but they do produce loss of appetite, nausea, and diarrhea. In addition, necrosis of the region of the kidneys and the ureters have been observed. One to two weeks after the initiation of treatment, the lymphocyte and granulocyte counts decrease, followed later by the thrombocyte and erythrocyte values. In about 50% of the cases, the hair on the head falls out and less often body hair is lost as well. This loss of hair is usually reversed after 2–3 months in spite of continued treatment. The occurrence of unexpected side effects should be taken into consideration as well, as for example, the appearance of pulmonary fibrosis, as a result of treatment with busulfan.

Indications

These compounds produce certain favorable effects in polycythemia vera, lymphogranulomatosis, lymphosarcoma, and chronic lymphatic or myeloid leukemia. Orally active preparations have properly replaced nitrogen mustard to a large extent. Nevertheless, even with these compounds, therapy is generally initiated with intravenous injections, i.e., cyclophosphamide, 2–6 mg/kg daily for 6 days. The maintenance dose is adjusted to produce a leukocyte count of 2000–5000/mm³. This generally requires doses of 50–200 mg daily by mouth. Because of the potential danger of the formation of secondary tumors, these compounds should be used in immunosuppressive therapy only after the risk involved has been carefully considered.

Antimetabolites

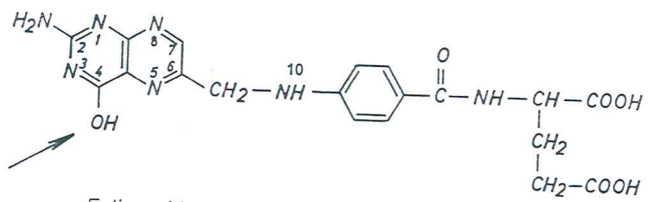
Folic Acid Antagonists

Folic acid antagonists are closely related chemically to folic acid. They displace folic acid from its site of action in the cell, interfere with the conversion of folic acid into its biologically active form, tetrahydrofolic acid, and competitively displace tetrahydrofolate from its site of action in the synthesis of nucleic acids. These effects are seen most prominently in the less differentiated, early stages of white blood cell development and also in the epithelial cells. Therefore, damage to the bone marrow, ulcerations of the mouth and gastrointestinal tract, and severe skin reactions can easily occur. The effects of these antagonists can be overcome by administration of folinic acid, N^5-formyl-tetrahydrofolic acid (citrovorum factor), but not by folic acid.

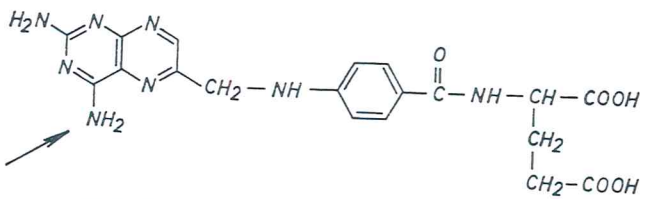
These compounds when administered during pregnancy to man and experimental animals produce death and resorption of the fetus, since the chorion requires particularly large amounts of folic acid. There are cases in man in which deformed

infants have been born when the fetus was not killed as the result of the administration of these compounds.

The most widely used compounds of this group are aminopterin in which the OH group in the folic acid molecule has been replaced by an amino group and N^{10}-methyl aminopterin (methotrexate). In some cases of acute leukemia in children both drugs have produced transient remissions. Single doses of aminopterin are 0.25–0.5 mg orally or intramuscularly.



Folic acid
Pteroylglutamic acid

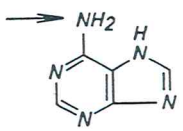


Aminopterin
4-Aminopteroylglutamic acid

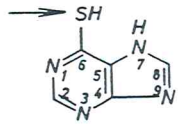
Purine antagonists are purine derivatives which essentially act as do the folic acid antagonists, because they also interfere competitively with nucleic acid synthesis. 6-Mercaptopurine is a competitive inhibitor of reactions involving 6-aminopurine (adenine) and 6-hydroxypurine (hypoxanthine), both of which are required for nucleic acid synthesis. Correspondingly, remission of acute leukemia in children has been obtained with 6-mercaptopurine. The toxic effects are as serious as those occurring after folic acid antagonists. In other diseases the activity of mercaptopurine is not predictable or it has none at all. The dose is about 2.5 mg/kg by mouth which can be increased later. Another purine antagonist, azathioprine [6-{(1-methyl-4-nitroimidazol-5-yl)thio} purine] has primarily found use in immunosuppressive therapy.

5-Fluorouracil acts as a uracil antagonist and its activity can be considered to be that of a purine antagonist.

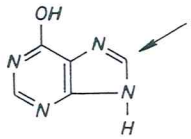
Allopurinol inhibits the degradation of xanthine and hypoxanthine to uric acid by inhibiting xanthine oxidase. It possibly also has effects on purine synthesis. This drug is not a cytostatic agent but is used in the treatment of gout (cf. p. 143). In cases of marked cell destruction as the result of cytostatic therapy, allopurinol is capable of maintaining reduced uric acid levels.



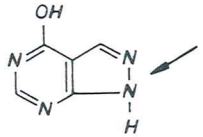
Adenine
6-Aminopurine



6-Mercaptopurine



Hypoxanthine



Allopurinol
1H-Pyrazolo[3,4-d]
pyrimidin-4-ol

Other Inhibitors of Mitosis

Colchicine is an alkaloid obtained from the autumn crocus, *Colchicum autumnale*, that has been used successfully for a long time against acute attacks of gout (cf. p. 143). In addition, colchicine has an effect upon cell division. It arrests mitosis in metaphase so that numerous spindles can be visualized histologically at this stage, especially in tissues with rapid cell division. The hope that this inhibitor of mitosis might represent a selective antitumor drug has not been fulfilled. The therapeutic index is too small.

Two alkaloids, vinblastine and vincristine, have been obtained from the periwinkle plant, *Vinca rosea*. The former is used in cases of lymphogranulomatosis and choriocarcinoma; the latter, in acute leukemia. These compounds appear to be inhibitors of mitosis. The side effects correspond to those of other cytostatics; in addition, disturbances in the function of the peripheral nervous system can occur.

Arsenic trioxide is an inhibitor of mitosis but also possesses carcinogenic activity.

Enzymes

Certain neoplastic cells, including leukemic cells, require asparagine from the extracellular space since they do not possess the capacity for asparagine synthesis. If the tissue levels of asparagine are markedly reduced by the administration of L-asparaginase, an inhibition of the growth of the neoplastic cells occurs. In some cases of leukemia, especially acute lymphatic leukemia, transient success has been obtained with the administration of L-asparaginase. However, the development of

resistance occurs rapidly. Furthermore, such therapy is burdened with considerable side effects (vomiting, fever, edema).

Hormones

Glucocorticoids frequently result in transient improvement in cases of acute leukemia in children and sometimes also chronic adult leukemia.

Estrogens can slow the growth of prostate carcinomas and their metastases in many cases and alleviate or eliminate the pain. Life expectancy can be prolonged. Since castration enhances the effect of the estrogens, the therapeutic effect is attributed to the inhibition of androgen production as the result of an impairment of gonadotropin mobilization from the anterior pituitary gland. The tumors may regress considerably in many cases, although they do not disappear completely. Treatment must be continued over the patient's entire life span. The sensitivity of the tumor cells to estrogen decreases with time. The dosage of diethylstilbestrol dipropionate is initially 3–7 mg orally per day, later 1.5–3 mg. Diethylstilbestrol diphosphate can be administered intravenously in considerably higher doses.

Androgens are effective in only some cases (about 20%) of mammary carcinoma. Estrogens appear to be more effective against metastases as well as primary tumors which develop some years after the occurrence of menopause. The attempt has also been made following the surgical removal of mammary carcinomas to inhibit the development of metastases by androgens or estrogens and even alkylating agents of the nitrogen mustard group. Testosterone esters with their long duration of action are suitable, i.e., testosterone enanthate initially given intramuscularly every 2 weeks and later every 3–4 weeks. Virilization must be expected with such treatment. Testolactone, a lactone derivative of testosterone, possesses no androgenic activity. However, its inhibitory effect on mammary carcinoma corresponds to that of testosterone.

CHAPTER 9

LOCAL THERAPY OF THE SKIN

Only those drugs will be discussed in this chapter that are typically used in dermatological therapy, and not those agents which have been presented elsewhere and are, of course, also used by dermatologists for local or systemic therapy. Thus the local application of an antibiotic, a corticosteroid, or antihistamine is not included, although of course these agents have their place in dermatology. Rather, a very brief discussion of ointment bases and their composition, the use of which rests primarily upon an empirical base, will be presented.

Inert Materials

Inert substances can serve two functions: (1) on the basis of their typical properties they can protect, dry, oil, or cool the area of skin to which they are applied as powders, ointments, pastes, or solutions; and (2) they can serve as a vehicle for the application of various drugs. The choice of the inert material (which despite the term need not be "inert") is determined by the therapeutic goal sought and the individual circumstances (skin type, nature of the disease, etc.). Ointment bases can be classified as follows.

1. Water-repellent bases. Paraffins, vaseline, or lard are suitable for the preparation of these bases. They serve to protect the skin, and active ingredients generally penetrate poorly from such a base into the skin.
2. Anhydrous, water-absorbent bases. These consist of anhydrous wool fat or anhydrous eucerite. The addition of emulsifying agents adds to these basically water-repellent materials the capacity for taking up water.

3. Water-oil emulsions. These are designed either as water in oil emulsions or, vice versa, as oil in water emulsions. The emulsified ointment bases have a cooling effect upon the skin by promoting the evaporation of water and are easily removed by washing. Drugs contained within them are easily absorbed by the skin.
4. Water-soluble ointment bases. These consist either of polyethylene glycols or hydrate colloids in glycerol-water. They have a jellylike consistency. This type of base also is important in cosmetics as a fat-free ointment.

Active Materials

Drugs producing hyperemia are widely used, particularly by the lay public to affect deep-seated diseases such as arthritis, neuritis, etc. Even if the usefulness of such treatment is questionable, such counterirritants are certainly not without a psychotherapeutic benefit. Agents which have found historical use and produce marked irritation such as cantharides (from the Spanish fly, *Cantharis vesicatoria* and related species), oil of mustard, or capsaicin (from *Capsicum* species) are today obsolete. Essential oils and their constituents such as camphor and eucalyptol can be used; but derivatives of nicotinic acid, such as the benzyl or butoxyethyl ester are to be preferred. While in high concentrations, chrysarobin and anthralin are irritants; in low concentrations, they are used primarily against psoriasis. Tars are applied to chronic dermatoses, especially eczemas; apart from an antiinflammatory effect, they have an antiinfectious activity and stop itching. Coal tar, wood tar, and other tars may all be used. Ichthammol is used similarly to tar. It is supposed to speed the healing of boils, and can be applied to mucous membranes (vagina or rectum). Menthol in alcoholic solution is suitable for the local treatment of itching. It also has a cooling effect. Salicylic acid has a keratolytic effect; in dilutions of 2–10% it softens horny layers of the skin and removes calluses. For cauterizing excessive granulation tissue, metal salts (silver nitrate) and strong acids (chromic acid, lactic acid, trichloroacetic acid, and concentrated acetic acid) are suitable. A mixture of lactic acid (10%) and salicylic acid (10%) in collodion is very suitable for the local treatment of corns. In order to protect the skin from ultraviolet radiation, compounds are used that absorb this radiation or transform it into light of a longer wavelength, which in turn produces pigmentation. A 2% stabilized hydroquinone salve is effective for the depigmentation of hyperpigmented areas of the skin. Short-term application of calcium or barium sulfide is used for depilation. Disinfectant agents suitable for local application to the skin and mucous membranes are discussed elsewhere (cf. pp. 252–261).

CHAPTER 10

GENERAL PHARMACOLOGY

The Scope of Pharmacology

Depending on one's point of view, the term "pharmacology" can be defined in a wide or narrow sense. The most comprehensive definition could read as follows: "Pharmacology is the science concerned with the action of chemical compounds on living systems." However, this definition is certainly too general and therefore unsatisfactory. On the other hand, a definition such as "Pharmacology is the scientific discipline concerned with the action of therapeutic agents" is too narrow and includes only certain aspects of pharmacology, since the expression "drug" comprises more than the expression "therapeutic agent." The expression "drug" is defined by the World Health Organization as follows: "A drug is any substance or product that is used or intended to be used to modify or explore physiological systems, or pathological states for the benefit of the recipient." A "therapeutic agent" should be defined as follows: "Therapeutic agents are biologically active compounds or mixtures of compounds that when employed appropriately according to medical science, are suited (a) to demonstrate, abolish, diminish, or prevent pathological phenomena, (b) to demonstrate or influence organ structures, organic functions or behavior of man or animals, as far as medical or veterinary purposes are served."

It is not possible to sharply differentiate pharmacology from other related disciplines; nor can it be characterized by its methodology. Modern experimental pharmacology has adopted techniques from a large number of other disciplines (e.g., physiology, biochemistry, radiochemistry, biophysics, endocrinology, microbiology, and histology) without developing specific pharmacological methodology

or even being primarily interested in such development. We rather believe that pharmacology can be characterized only by the nature of the questions asked: where, how, and why a compound acts is investigated in order eventually to obtain a useful drug or to explain the mechanism of action of a drug. These aims are served by descriptive pharmacology and basic pharmacological research even if the individual experimental steps appear to have only a distant relationship to therapeutic application. Therefore, the aim of pharmacological research is not the collection of data for itself, but rather ultimately in order to help man and animals. In principle, there is no difference in concept or methods between pharmacological and toxicological research. On the contrary, it is but a short step between the two fields. Such a conclusion must necessarily be drawn since actually every compound can be a poison if it is administered in sufficiently high doses. ("*Dosis sola facit venenum.*")

As soon as a new compound of possible medical interest becomes available, its descriptive pharmacology is first dealt with; what the compound *does* is investigated and described. Simultaneously, its descriptive toxicology is investigated: *How* toxic is the compound and what symptoms occur? The next step should be basic pharmacological and toxicological research; the question to be answered is *why* the compound has its particular activity and toxicity. Such knowledge goes beyond simple empiricism and leads to an understanding of the mechanism of action. It goes without saying that, in general, it is difficult to actually elucidate a mechanism of action. Methodology and knowledge from physiology, biochemistry, biophysics, and microbiology, etc. are required in order to comprehend these basic occurrences on the cellular or subcellular level. As the reader of this book has seen, the mechanism of action is known for only a small number of compounds (e.g., cholinesterase inhibitors, neuromuscular blocking agents of the depolarizing type, osmotically-active laxatives, etc.), while it is unknown for a large number of other drugs which are very potent and irreplaceable. In this context only a few examples, such as endogenous compounds like the steroid hormones and oxytocin, and exogenous drugs such as cardiac glycosides, narcotic analgesics, and nitrites need be mentioned. From these considerations, it is obvious that pharmacology is a very young science which remains largely empirical.

Should it be suspected that a compound could be of therapeutic value, a new branch of pharmacology, clinical pharmacology, becomes of importance. On the basis of observations in experimental animals, the actual therapeutic effect is evaluated in man, using quantitative methods of investigation. In clinical pharmacology the experimental and clinical disciplines are allied.

Heuristic Principles of Pharmacology

There are two principles which always confront those concerned with the action of drugs—receptor theory and structure-activity relationships.

Receptor theory is based upon the concept that a drug can be active on the

cellular level only if there is some type of molecular reaction partner present. This reaction partner (receptor) must have certain specific properties in order that it can enter into a chemical bond (the type of which is of no importance for the concept) with a particular compound or group of compounds. The consequent physicochemical changes in the local biological properties involved at the site of action are transformed into a "stimulus" that finally elicits the "effect." The principal types of bonds involved are: hydrogen bonding, apolar bonds (van der Waals' forces), ionic bonds, and covalent bonds (cf. for example, the postganglionic acetylcholine receptor, Fig. 9; the active center of the cholinesterase, Fig. 10; and the norepinephrine receptor, Fig. 11). It is possible to characterize a particular receptor by describing the properties of the compounds which react with it. The receptor itself is then, so to speak, a "negative replica" of these compounds. In this way, one has been able to obtain certain conceptions of the nature of the acetylcholine, norepinephrine, and histamine receptors. However, the active centers of enzymes are also considered to be receptors, e.g., the active sites of cholinesterase are receptors for the compounds acetylcholine, physostigmine, and for the esters of phosphoric acid. For the initiation of a certain stimulus, the number of binding sites occupied is probably not decisive, but rather the number of receptors occupied per unit of time, which is the turnover number. Highly active agonists are characterized by a high rate of association and dissociation. Furthermore, the picture of the receptor may be used to clarify the competitive antagonism between two compounds. Agonists are compounds which combine with the receptor and produce a change in cellular properties (high affinity and "intrinsic activity"); competitive antagonists combine reversibly with the same receptor, but produce no change (high affinity; lack of "intrinsic activity"), and thereby block receptors so that the agonist becomes inactive (e.g., acetylcholine-atropine, acetylcholine-*d*-tubocurarine; epinephrine-sympatholytics, histamine-antihistaminics). Agonists and antagonists compete for the same receptor and accordingly one compound can be displaced from the receptor by an increase in the concentration of the other compound.

Along with competitive antagonism already presented, other types of antagonism may be classified as noncompetitive, functional, and chemical antagonism. The various types of antagonism and their characteristics are summarized as follows.

1. *Competitive.* Antagonist and agonist compete for the same receptor. The antagonist combines with the specific binding site in a reversible manner and can be displaced by the agonist according to the law of mass action. Examples: acetylcholine-atropine (smooth muscle, glands), histamine-antihistamines, *p*-aminobenzoic acid-sulfonamides.

2. *Noncompetitive.* In contrast to competitive antagonism, under the term "noncompetitive" are brought together quite different antagonistic mechanisms of action. A noncompetitive antagonist does not necessarily react with the specific receptor of the agonist, but it may block the sequence: receptor→stimulus→effect at various sites. An increased agonist concentration cannot overcome this type of antagonism. (a) The association of a drug active as an antagonist in the *neighborhood* of the receptor may induce a change in the specific steric structure (conformation) of the receptor, so that an agonist no longer fits in an optimal manner to this structure and its effect is accordingly diminished (allosteric antagonism). (b) The site of attack of the noncompetitive antagonist may lie beyond the agonist-receptor level and interfere with the initiation of the stimulus or the effect (papaverine, see p. 43). (c) Also classified as noncompetitive are those antagonisms in which an irreversible (covalent) combination of the antagonist with specific or nonspecific binding sites takes place (organophosphates and cholinesterase). The phase during which the association of irreversible antagonists takes place may still be influenced competitively.

Functional Antagonism

This type is characterized by the fact that the agonist and antagonist have different cellular sites of action; however, the diametrically opposed activities elicited are in one and the same tissue. An example is histamine-norepinephrine (blood pressure). (Take note that formally, the concentration-effect curves can be identical for functional and noncompetitive antagonism.)

Chemical Antagonism

With such antagonisms the chemical reaction between two drugs (possibly the poison and antidote) can take place independently of the organism. Examples are heparin-protamine (anticoagulant) and mercury-dimercaprol (toxicity).

Structure–activity relationships actually are derived from the concept of the receptor, for if the receptor is thought to have certain chemical, physicochemical, and physical properties, then naturally another requirement must be that the agonists possess restricted complimentary structures. It has indeed been possible to show for a whole series of compounds the particular structural properties which must be present in order to achieve a particular activity. Such knowledge is, however, at the moment very restricted so that in general the structure–activity relationship can at first only be interpreted retrospectively on the basis of empirically obtained findings. Predictions concerning a particular biological activity of a chemical compound must be made with great caution. On the other hand, another procedure (a type of degenerate structure–activity principle) is frequently practiced for commercial reasons in order to obtain so-called analog preparations. If a compound has been recognized to possess activity, an attempt is made to change that portion of the molecule not essential for activity. Examples of this approach are seen with the antiepileptic drugs (in which it is unimportant that if besides the four atoms which are necessary for activity, the fifth atom in the ring is a carbon atom, nitrogen atom, or oxygen atom); the hypnotics (barbituric acid or pyrimidine-dione derivatives); psychopharmacological agents (irrelevant changes in the ring system and in the side chain at position 10 of phenothiazine), the saluretics, etc. (cf. the con-

responding structural formulas). New basic knowledge can hardly be expected with such procedures; it is obtained accidentally, if at all.

General Principles of Pharmacology

Dose-Response Curves (Concentration-Effect Curves)

The dependency of the response upon the dose or concentration of a drug is a characteristic function of every compound, and is exhibited by the dose-response curve. Frequently used parameters are: abscissa, the dose or concentration in logarithmic units; ordinate, the response in percent of the maximum possible response.

Two characteristic examples from experimental medicine demonstrate this dependency. Figure 61 shows the results of an experiment on the isolated ileum of the guinea pig. Two compounds with suitable affinity and "intrinsic activity" have been compared. The figure shows that one compound (acetylcholine) possesses a higher affinity, i.e., it is active in greater dilution than the other compound (arecoline). The latter has a higher "intrinsic activity" since the maximal possible effect is greater. In Fig. 62 a dose-mortality curve is presented which is the result of the examination of the acute toxicity of metamphetamine in mice at two differing environmental temperatures. A steep running curve was obtained from experiments at 25°C. The dose at which 50% of the animals died (LD_{50}) is about 150 mg/kg. With an environmental temperature of 30°C, the toxicity of the compound is considerably increased (LD_{50} approximately 40 mg/kg). In addition, the curve is flatter, i.e., the dose range in which a particular effect is obtained becomes larger and therefore the appearance of an expected activity more unsure. This experimental example also demonstrates the degree to which the activity of the drug can be dependent upon environmental conditions.

The problems which occur in evaluating a drug in relation to its therapeutic index and in comparing two drugs are illustrated by the following example

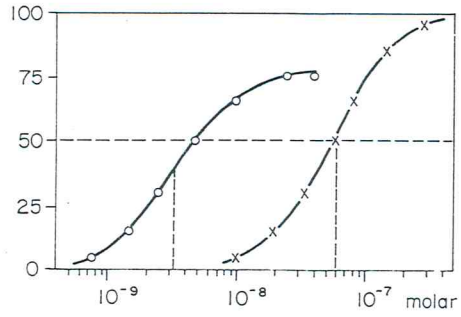


Fig. 61. Dose-effect curves for acetylcholine (O—O) and arecoline (×—×) on the isolated ileum of the guinea pig. Abscissa: molar concentration in logarithmic units; ordinate: effect in percent of maximal possible shortening. For details see the text.

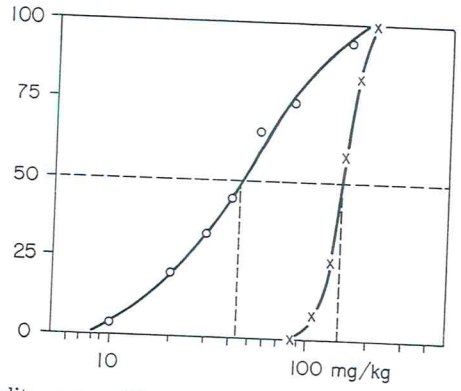


Fig. 62. Dose-mortality curve. Metamphetamine, subcutaneous injection in male mice. Abscissa: dose in milligrams per kilogram in logarithmic units; ordinate: percent animals killed. Environmental temperature. ×—×, 25°C; O—O, 30°C. For details see the text.

(cf. Fig. 63). Curves I and II are the concentration-activity curves of two compounds (A and B) which both possess the same ED_{50} of 10^{-7} M (or gm/ml). The abbreviation, ED_{50} (effective dose 50%), is the dose (or concentration) which leads to an effect which is 50% of the maximal or in which the expected result occurs in 50% of all cases. As valuable as this parameter may be for the comparison of compounds, it says nothing concerning the slope of the curve. Although curves I and II exhibit the same ED_{50}, they are considerably different, if the mortality curves of compounds A and B are taken into consideration. Curve III corresponds, as does curve I, to compound A; the LD_{50} is about 10^{-4} M or gm/ml. The LD_{50} is the dose (concentration) at which 50% of the experimental animals die. Compound A is

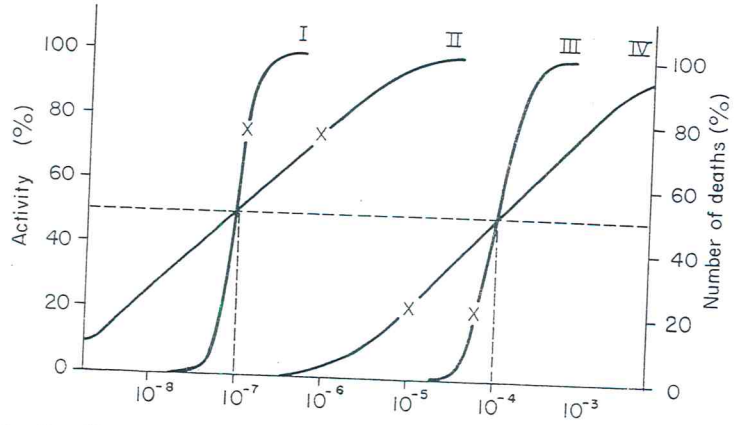


Fig. 63. Graphic representation of concentration-effect curves or concentration-mortality curves (see the text for details). Abscissa: concentration (M or grams/ml) in logarithmic units; ordinate: effect or number of lethal cases in percent of the maximum possible. The ED_{50} and LD_{50} are indicated with crosses. Curves I and III correspond to compound A; curves II and IV compound B.

characterized by the fact that a small increase in the concentration is accompanied by an extraordinary increase in the effect or in mortality (steep dose-response or dose-mortality curves). Compound B behaves differently; just as for the dose-response curve, the mortality curve (IV) is very flat. This means that an increase in the concentration elicits only a small increase in the response or mortality. Nevertheless, the LD_{50} is the same as that of compound A.

The importance of the steep or flat curve becomes immediately clear if one observes from the diagram what the situation will be if a maximal effect is to be elicited with compound A or compound B. A concentration of about 3×10^{-7} is required for 100% activity with compound A; the minimum lethal dose (LD_{10}) is about 3×10^{-5}. There is therefore a safety margin of about two orders of magnitude. For compound B, maximal activity is achieved at 10^{-5} which already corresponds to an LD_{20}, i.e., if one wishes to obtain the maximal effect, 20% of the experimental animals will die. Therefore, with compound B it is not possible to obtain maximal activity without endangering the animal. What can be said of this animal experiment is particularly true in pharmacotherapy; only compound A would be suitable as a medicinal agent (sufficient therapeutic index).

Therapeutic Index

The margin of safety referred to above is called the therapeutic index. Quantitative values for the therapeutic index which are obtained from animal experimentation are the quotients from points on the dose-mortality and dose-response curve. Thus, the therapeutic index is frequently defined as Th.I. = LD_{50}/ED_{50}. The larger the value, the farther the two curves are separated from one another and the larger the therapeutic index. However, this value has one gross disadvantage, in that it correctly depicts the relationships only if all the curves are parallel. As soon as there is a difference in the slope, the therapeutic index defined in this manner is no longer a measure of the margin of safety, as was seen in the example above with compounds A and B. Both compounds had the same therapeutic index, which led to a completely false conclusion. In comparing compounds with nonparallel dose-response curves, another parameter is a much better measure of the two relationships. The collection in Table XI of such parameters from our example illustrates this point.

TABLE XI

Ratios to Characterize the Therapeutic Index[a]

Compound	$\frac{LD_{50}}{ED_{50}}$	$\frac{LD_{25}}{ED_{75}}$	$\frac{LD_{10}}{ED_{90}}$
A	1000	~500	~250
B	1000	~10	~0.25

[a] See text.

Since for experimental reasons there is greater uncertainty as to the correct values of the LD_{10} and LD_{90} than there is for the LD_{25} and the ED_{75}, the quotient LD_{25}/ED_{75} is probably the best possible parameter for assessing safety; in any event the quotient LD_{50}/ED_{50} simply gives a false answer as to the safety of the two drugs since both compounds A and B have the same quotient.

While in animal experimentation the therapeutic index is derived from mortality curves, in clinical therapy it is related to the dose-toxicity curve (due to important side effects) which at least formally offers as good a system of reference as the mortality curve. At this point a relationship should be emphasized that can be derived directly from the therapeutic index but which is often overlooked, particularly in drug advertising. For therapy, one is not interested in the absolute potency (dose in grams or milligrams) of a compound, but in the therapeutic index. For this reason the expression "the new compound X is two times as active as the previous drug Y," is completely uninformative. The decisive statement would be "the new compound X has a therapeutic index two times as great as that of the previous drug Y."

Mechanism of Action

The mechanism of action of a drug designates the biochemical and biophysical changes caused by the compound in question that are the basis for its gross effects. It is the elucidation of the causal chain of events which produces its overall activity (or the satisfaction of the human desire to coordinate and classify observable phenomena with a general system of natural laws). The mechanism of action explains the activity of a compound on the basis of its interaction with known physiological or biochemical processes. In this way knowledge of the activity of the drug is raised from the empirical-descriptive level to one in which it can be understood within a clearly defined frame of reference; the mechanism of action makes the drug effect understandable. Didactically this means that the learning of facts is replaced by the understanding of principles. For this reason we have attempted in this textbook, wherever possible, to present the mechanism of action or at least some known relationships, in order to facilitate understanding.

Skeptics may object to such explanations, for example, as follows: inhibition of the peripheral sympathetic nervous system by reserpine can be explained as the result of the loss of the ability to store norepinephrine; or the immediate neutralization of an overdose of heparin by injection of protamine can be explained by the formation of a salt between the two compounds. However, is this really an explanation? The following questions remain open: Why does reserpine inhibit the storage capacity, and why does acidic heparin form a salt with basic protamine? To such an objection one can only answer that of course the causal chain is never at an end and pharmacology is not differentiated in this respect from the classical scientific disciplines. Nevertheless, we maintain that there are important differences between the statements given above concerning the mechanisms of action of reserpine or protamine and those in the following examples. Physical and psychic masculine sex characteristics are dependent upon testosterone; or morphine inhibits pain perception. Even tentative explanations

Biological Variation

If repeated measurements of the same parameter yield values that are not identical but are grouped around an average point, this phenomena is called variation. The calculated mean value is not sharply defined; it exhibits an uncertainty. A quantitative expression for this is the variance (the sum of the deviations squared divided by the number of measurements minus 1:

$$\frac{\sum x^2}{n-1} = s^2 = \text{variance}$$

or the standard error of the mean $s_{\bar{x}} = s/\sqrt{n}$.*

Biology and therefore also medicine and, in special cases, experimental and clinical pharmacology are in a completely different situation than the classic scientific disciplines. In the latter, the variation is exclusively determined by the measurement process. Naturally, such variation is also present in biology, but it is small in relation to the variation which is engendered by the fact that biology deals exclusively with individuals. The difference between single individuals always becomes larger the more differentiated the species; correspondingly, the biological variation also is larger. In part, individual differences are genetically determined; in part they are engendered by the environmental conditions. The extreme case is seen in man in which the physical and psychic differences between individuals appear to be greatest. An everyday observation indicates how different the reaction to one and the same drug can be: a nonsmoker can become "sick" if he must stay for only a short time in a room in which there is smoking, while another individual becomes "sick" if he cannot smoke at least 60 cigarettes per day!

The large biological variation with which experimental pharmacology and even more so, clinical pharmacology, have to deal imposes a heavy experimental burden. A single experiment or a single clinical observation cannot be considered as evidence; only statistical analysis can result in reproducible and thereby established results. On the other hand, statistical methods do not offer the last word. The single observation is important but testing its reliability certainly always requires a number of experiments or observations under identical conditions (cf. p. 329).

Uptake, Distribution, and Excretion of Pharmacological Agents (Pharmacokinetics)

Routes of Administration

A drug can exert its effect only if it reaches its site of action, which is but rarely at the surface and readily accessible. The drug for this reason must be taken up into the tissues; it must be absorbed. This also holds true for topical therapy since generally the active compound must penetrate the skin or membrane surface to the site of action. Examples of the latter are found in local anesthetics, the membrane-shrinking sympathomimetics, the bronchodilator agents that are inhaled, etc. In these cases the drug must penetrate from the surface to the sensory receptors, into the smooth muscle of the vasculature, or to the bronchi, respectively.

* x = deviation of single measurement (x) from the mean ($\bar{x}$). $\bar{x}$ = mean value; and n = number of single measurements.

Absorption is always of importance if the drug is not injected directly into the bloodstream. It consists of the physical process of diffusion associated in many cases with active biological processes (e.g., the energy-requiring transport of potassium, selective transport of sugars). The rate of absorption is dependent upon the site of application and the physicochemical properties of the drug. The absorption of the single drug molecule is considered to be complete when it reaches either the local site of action or the bloodstream. The following properties accelerate absorption: small molecular size, lack of polarity, good water or fat solubility, marked blood flow, and good permeability relationship at the site of application. The opposite properties diminish the rate of absorption. This can be utilized in depot preparations. The drug is prepared in a poorly soluble form and injected as a suspension (procaine penicillin, protamine-zinc-insulin, etc.) or it can be maintained at the proper site through the addition of vasoconstrictor agents (local anesthetic with epinephrine).

Topical therapy is characterized by the fact that the drug concentration is only effective at the site of application while the absorbed quantity of drug remains below the threshold for activity in the rest of the body. The possibilities of topical therapy are not restricted to the skin but are considerably greater. The inhalation of a bronchodilator agent, the oral administration of activated charcoal for the adsorption of poisons in the intestine, or the injection of a glucocorticoid into a joint are examples of topical therapy. The systemic effects with topical application can usually be neglected, and therefore this route of administration is characterized by a large therapeutic index. Nevertheless, it also has its disadvantages (e.g., the easy development of allergy upon application to the skin and mucous membranes).

The most frequent mode of administration for a drug is the oral route. Absorption is particularly dependent upon the form in which the drug is taken (powder, tablet, capsule, solution, or syrup), the properties of the drug, and the functional state of the gastrointestinal tract. Following administration, the drug passes through the liver (portal circulation) in which it may be altered. If the drug is taken up through the mucous membranes of the mouth and esophagus (buccal or sublingual route) and with rectal administration, it is not transported by the portal circulation. From practical experience it is known that after rectal administration the concentration in the blood is unpredictable in individual cases and generally, is considerably lower than usually assumed. If a compound is rapidly degraded in the liver, a considerable quantitative difference can exist between its effects following sublingual and enteral administration. A disadvantage of oral administration is that many drugs are destroyed in the gastrointestinal tract before they can be absorbed. Since this occurs in a not always predictable fashion and absorption is dependent upon a series of other factors (contents and pH of the stomach and small intestine, presence of bile, etc.), the amount absorbed can only be estimated with great uncertainty (e.g., ouabain).

Parenteral administration avoids the disadvantages of the oral route, but requires sterile injection technique and a solution which is close to isotonic with blood. The most rapid drug distribution is achieved with intravenous in-

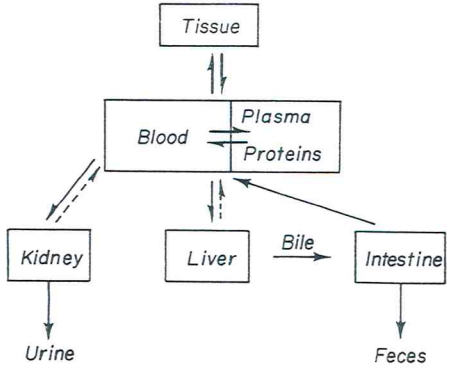


Fig. 64. Schematic representation of the distribution and elimination of drugs. When a drug has passed into the blood (after enteral absorption or after parenteral administration) it is distributed between blood and tissues. Solubility, molecular size, and electrical charge mainly determine this distribution. The drugs pass into the primary urinary filtrate by glomerular filtration (up to a molecular weight of 70,000) and by tubular secretion. Lipid-soluble drugs are usually reabsorbed in the tubule and thus cannot be excreted via the kidneys. The main site of degradation of drugs is the liver. The drugs and their metabolites (whose water solubility is usually better than that of the parent compound), can be excreted with the bile. The products either leave the body in the feces or are reabsorbed, directly or after cleavage, e.g. the glucuronides (enterohepatic cycle).

arterial, or intracardiac administration. As the result of the considerable blood flow in muscle and the large surface area of the peritoneum, compounds are very rapidly absorbed following intramuscular and intraperitoneal injection. A noticeably longer time is required following subcutaneous injection.

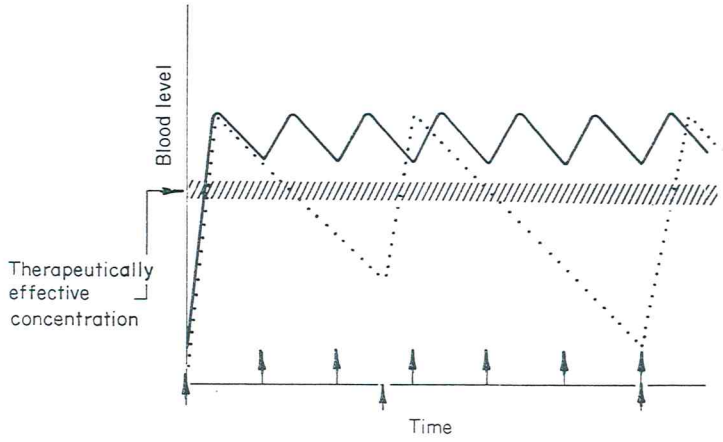


Fig. 65. Schematic representation of the dependency of the blood level of a drug upon the dosage regimen. The frequent administration of small amounts after a larger initial dose maintains the blood concentration higher than the therapeutically effective concentration; the administration at longer time intervals allows the blood level to fall below the therapeutically effective concentration.

Another mode of application for certain types of drugs is inhalation, which is particularly suitable for the gas and vapor anesthetics. Absorption is very rapid.

Distribution

The distribution of drugs within the body is dependent upon an entire series of factors represented schematically by Fig. 64. Some of these factors are the extent of the blood supply (e.g., the redistribution of thiobarbiturates from the brain into fat tissue); the ratio of the water to fat solubility (e.g., accumulation of chlorophenothane in fat tissue), tissue-specific accumulation (e.g., iodine in the thyroid or lead in the bones); binding to protein or other large molecules (plasma protein binding); and the ability of the drug to penetrate membranes. The size of the volume of distribution of the drug is dependent upon these factors. It can be small if a drug does not leave the vascular system (the dye Evans blue, dextran, etc.); it may be approximately coextensive with the size of the extracellular space (e.g., sulfate ion); or it can correspond to the volume of total body water (ethanol, antipyrine, etc.). In addition, penetration of membrane barriers such as the blood–brain barrier, the placenta, or the mammary glands by a particular compound is dependent upon its permeability properties. Finally, of course, the distribution is influenced by the rate of absorption and the rate of elimination of the compound.

The distribution of the drug in the body is only very rarely at the steady state, namely when continual administration over a long period of time exactly equals the amount being eliminated. In clinical and experimental pharmacology such a steady state is very difficult to obtain (the exceptions are the extremely long-acting depot preparations such as hormone implants). In general, such a steady state is not achieved because the administration of the drug is discontinuous. This results in an oscillating blood and tissue drug level. However, this is acceptable if the drug concentration does not fall below the minimal effective therapeutic concentration (Fig. 65).

Elimination

The term "elimination" includes all processes which are associated with the inactivation of a drug effect: excretion by various organs and chemical changes in the molecule. The half-time for this process is frequently given as a measure for the rate of elimination. This is the time required for the drug concentration to decrease to one-half of its initial value. It is a biological quantity which should not be confused with a physical quantity such as the half-life of a radioactive isotope. For a radioisotope present in the body, both the biological and physical half-life must be considered.

Drugs can be excreted in various ways. Generally the largest amounts of the original drug or its metabolic products appear in the urine and feces. Compounds possessing good lipid solubility are rather poorly excreted by the kidney since continual reabsorption occurs during their passage through the renal tubules. Compounds reach the feces either by being excreted with the bile or by being

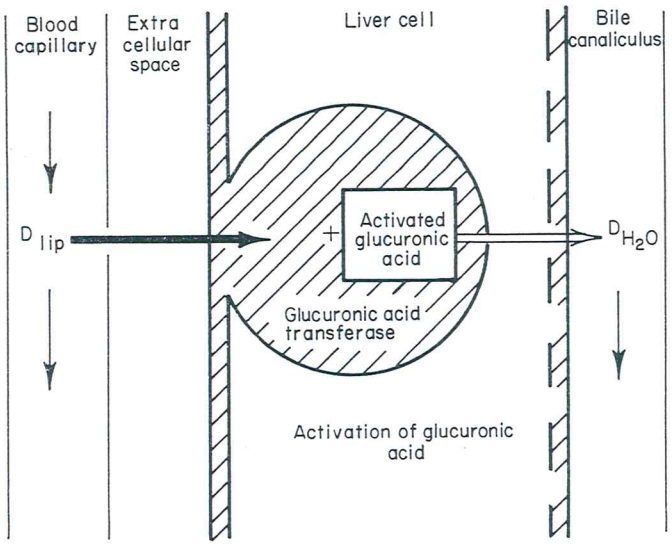


Fig. 66. Schematic representation of the excretion of a lipid soluble drug (D_{lip}) by the liver into the bile. On the basis of its lipid solubility, D_{lip} passively accumulates in the lipid-containing compartment of the liver cell. There it can be conjugated with glucuronic acid (increasing its water solubility, D_{H_2O}). The conjugate must passively leave the lipid compartment and accumulate in the water phase; in this case the bile fluid which can be reached without lipid barriers. The body in no way requires energy for the transport. It represents simply physicochemical distribution phenomena. Only the conjugation requires energy (namely, for the activation of the glucuronic acid). *Symbols:* Diagonals, "Lipid compartment" (coarsely dispersed *in vivo*); ➡, diffusion gradient for lipid soluble compounds; ⇒, diffusion gradient for water soluble compounds. The activation of glucuronic acid (uridine diphosphate) occurs in an aqueous phase; the transferase is localized in the lipid-containing microsomes.

or milk is of no quantitative importance. Elimination via the lungs is the most important route for some materials (anesthetics). Some drugs are concentrated at the site of their excretion and thereby achieve local toxic concentrations. An important example of such behavior is the kidney damage induced by mercury derivatives and phenols.

Corresponding to the large number of chemical compounds which are administered to the organism as drugs (or poisons), there is a very large number of possibilities for biotransformation which can lead to the formation of inactive or active metabolites. One speaks of detoxification if there is a chemical change in a poison which results in a loss of activity. However, the metabolic products to which a compound is converted may be more toxic than the drug itself (methanol to formaldehyde, the insecticide, Parathion (*O*,*O*-diethyl-*O*-*p*-nitrophenylphosphorothioate to diethyl-*p*-nitrophenylphosphate, etc.).

Some of the principal pathways of drug metabolism are

1. Cleavage and oxidation of small molecular fragments to carbon dioxide and water (e.g., paraldehyde, ethanol).

2. Partial degradation by decarboxylation or deamination (α-methyldopa, histamine, serotonin) or *N*-demethylation (aminopyrine, morphine, meperidine).
3. Oxidation or reduction (barbiturates, methanol).
4. Spontaneous or enzymic hydrolysis (succinylcholine, local anesthetics).
5. Conjugation with acids (acetylation of sulfonamides, conjugation with glucuronic acid). (See Fig. 66 in this connection.)

Most of the enzymes responsible for biotransformation are found in the liver, in particular in the endoplasmic reticulum or the microsomes obtained from this structure. The amounts of these enzymes can be increased by a large number of drugs from completely different chemical classes by enzyme induction. The result is an accelerated rate of degradation of the corresponding drugs. The change in liver function, however, has more far-reaching consequences since an increased enzymic activity also affects the degradation of endogenous compounds (such as sex hormones) and compounds of vital importance (like vitamin D): the concentrations of such compounds fall below their physiological level. It is obvious that the metabolism of other drugs that are not involved in eliciting the enzyme induction is accelerated. Examples of such enzyme inducers are barbiturates, chlorophenothane, hexachlorocyclohexane, tolbutamide, pyrazolon derivatives, and certain carcinogenic agents.

Apart from these possibilities, which are general and nonspecific, there exist specific degradative pathways for some drugs which are also important for endogenous compounds. Thus acetylcholine is hydrolyzed by the highly specific enzyme, cholinesterase, and norepinephrine is methylated by *o*-methyltransferase and rendered inactive.

For many of the above degradative processes, considerable sex differences have been shown to exist in experimental animals, but not in man. However, considerable differences in elimination rates of genetic origin sometimes occur in man. To mention an example, 10–30 fold variations in the blood level in various individuals have been observed after administration of the antidepressants desipramine and nortryptiline. Identical twins, on the other hand, showed identical blood levels. Similar results have been reported after the administration of dicoumarol, phenylbutazone, or phenazone. For practical therapy the following conclusions can be drawn.

1. A fixed dosage may cause effects of different intensity in different patients. In one individual the effect may not appear at all, in another individual the toxicity threshold may be surpassed.
2. If possible, determinations of the drug concentration in the blood should be carried out. Only this type of control would constitute a rational basis for the dosage of drugs for which such variations are known to occur.
3. Combination with a second compound should be avoided, especially if this may change the rate of elimination of the first drug.

Newborns and particularly, premature infants can be endangered by drugs because the liver is not completely equipped with enzymes and the rate of renal excretion is diminished

The rate of elimination of a drug is therefore considerably dependent upon the secretory and metabolic capacities of the liver and kidney. Every impairment of these functions results in a higher and more slowly falling blood level in comparison to normal conditions. This is associated with a longer duration of action, possibly toxic effects, and a tendency toward accumulation.

Cumulation

Cumulation is understood to be the slow increase in the tissue concentration of a drug occurring with administration at regular time intervals. It always occurs if more of a compound is administered per unit of time than can be eliminated in the same time. Correspondingly, every compound can cumulate; the only requirement is that the doses follow one another closely enough. However, in clinical usage one only speaks of cumulation if the drug is accumulated in the body even with a low frequency of administration (about one to two times daily). Examples of such compounds are barbital, digitoxin, lead, and chlorophenothane.

Additive Effects and Potentiation

These two terms describe the combined activity of at least two drugs (synergism). They are frequently used without sufficient precision which can, however, be obtained easily from a consideration of a dose-response curve. In Fig. 67 a typical dose-response curve is shown. Since the effect is not linearly dependent upon the dose, a doubling of the dose does not result in a simple doubling of the response. In the example, a unit dose elicits a response which corresponds to 15% of the maximum obtainable, but the double dose does not produce 30%, but rather

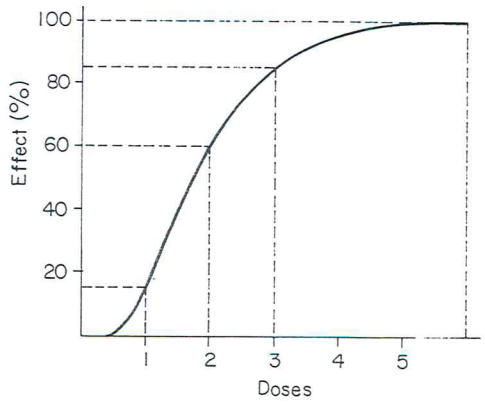


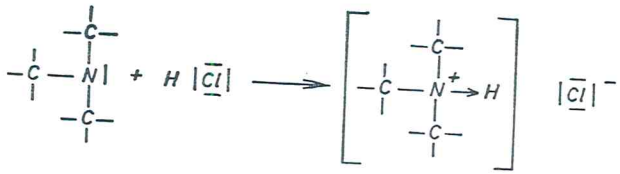
Fig. 67. Schematic representation of a dose-effect curve. Ordinate: effect in percent of the maximal possible effect; abscissa: dose in multiples of a unit. The effects of a single, two-, three- and sixfold dose are sketched in. See the text for details.

60% of the maximal effect. This doubling of the dose corresponds to an addition of the effects on the dose-response curve. In the ascending part of the curve the increase in response is larger than would be expected on the basis of a linear dependency. The reverse situation in which a smaller increase in the response is obtained with doubling of the dose is seen with the doubling of doses which already elicit more than 50% of the maximal activity. In the example, the threefold dose produces 85% of the maximal response; an additional doubling (sixfold) results in "only" a maximal effect instead of "170%" of the maximal effect. What is true of one compound must also be taken into account for combinations of two or more drugs. If with a combination of two pharmacological agents, the activity is larger than the linear addition of the activities of each compound alone, simple addition may be responsible. The question can only be answered on the basis of dose-response curves. The term "potentiation," which is much too frequently used, particularly in drug advertising, is meaningful only if the combination of the two compounds results in an effect larger than would be expected on the basis of the shape of the dose-response curves. Again with regard to the example, the following would have to be fulfilled in order for potentiation to be demonstrated: both unit doses of two compounds should produce 15% of the maximal effect while the combination of both should not result in 60% (cf. Additivity above), but 95%, for example. This would be potentiation. Such a phenomenon is extraordinarily rare.

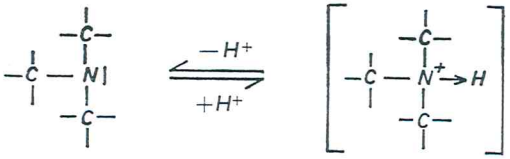
Tertiary Amines and Quaternary Amines

Many pharmacological agents are nitrogen compounds in which the nitrogen exists in the form of a tertiary or quaternary amine. Because of the importance of these naturally occurring (among others, alkaloids) and synthetic compounds, their chemistry will be briefly discussed.

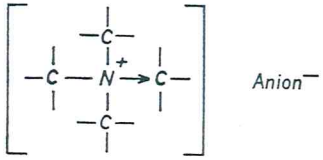
Tertiary amines are bases (compounds which covalently bond with protons); they form salts with acids.



As can be seen from the electron configuration (| means electron pair), the nitrogen atom in a tertiary amine possesses a free electron pair that can form a coordination bond with a proton. In such a case the nitrogen has four valences and is positively charged. The salt that is formed, for example, the hydrochloride, is always completely dissociated. The formation of a salt of a tertiary amine is dependent upon the pH of the solution and a characteristic value for each compound, the dissociation constant K. The negative logarithm of K is designated as the pK analogous to pH values. The pK is the pH at which 50% of the corresponding group is dissociated.

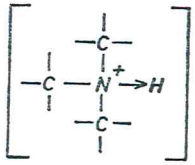


In a quaternary ammonium compound the four nitrogen valences are bound to carbon atoms and the nitrogen is positively charged.

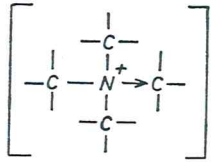


This salt is always dissociated. The positively charged nitrogen atom with four valences is considered to be an onium compound, regardless of whether it is a tertiary or quaternary amine.

For the physiological–pharmacological activity of an amine, it is of decisive importance if the nitrogen is in the onium form with four ligands or in the form containing three ligands. The following are equivalent as regards their biological activity:



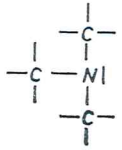
and



tertiary amine in salt form; 4-valence nitrogen, onium compound

quaternary amine, 4-valence nitrogen, onium compound

In contrast to the onium compound, there exists



tertiary amine in base form; 3-valence nitrogen; not an onium compound

Practical examples of these considerations can be found in the various chapters. However, of particular interest in this regard are the tertiary amines which are present at physiological pH values in both the three-ligand and four-ligand forms (pK in physiological pH range). An example of this are the local anesthetics. Only the free base is lipid soluble and can therefore penetrate into the nerve. On the other hand, the four-ligand form is probably active at the site of action. The poor

solubility of the onium compounds in lipids is exploited in a different context; while atropine as a base can penetrate easily into the central nervous system and thus lead to central toxicity; the quaternized form, methylatropine, has no central activity. However, both drugs must be in the four-ligand form for the actual parasympatholytic effect.

Introduction of New Drugs

The development of drugs proceeds at a rapid pace. Every year an uncounted number of new preparations becomes commercially available. At the time it is printed a textbook of pharmacology is outdated by 6 months to 1 year with regard to commercial preparations available. How then, should a physician react to a newly available compound? The answer is that the physician should inform himself on a scientific basis and reject all advertising slogans ("complex-specific," "potentiates endogenous defenses," "a complete therapeutic regimen within a single compound," "tissue detoxifying," "stabilization of the nervous system," etc.).* One should be very skeptical when it is maintained that a drug possesses no side effects; prescribe only preparations in which the qualitative and quantitative composition is known; and always look for the structural formula of a new drug. In this way one often can discover that one is dealing with an analog preparation while this might not be clear from the chemical name (cf. the benzothiadiazine group, p. 100). An analog preparation can be judged in first approximation as one would the parent compound. In the case that one is truly dealing with a new drug, it should be used only if the physician is informed concerning the effects and side effects. Only controlled clinical investigation can meet these prerequisites (see the next section).

If one maintains such a critical attitude, then one is on solid ground. We are convinced that the ethical pharmaceutical houses, who prefer to have in the physician an academic rather than a commercial partner, who must be influenced by unworthy advertising methods, will endorse these precautions.

Controlled Clinical Investigation of Drugs

Methodology

It has been shown with more exact testing that a drug which has been successfully used for a long time does not necessarily have pharmacological activity. The judgment of pharmacological effects in man is very difficult since the human takes the drug with expectation and hope. This psychological condition, which can be further strengthened by the suggestive personality of the physician, is

* All these phrases have been chosen arbitrarily from a single issue of a weekly medical journal. These slogans, collected 7 years ago, can even be observed nowadays

sufficient in and of itself in many cases for the alleviation of the complaint. In this regard not only functional disturbances of the central or autonomic nervous system are affected but also organic diseases may take a more favorable course. In addition, it should always be remembered that most common diseases heal spontaneously. These facts have been known to experienced physicians for a long time, but only recently have they been systematically investigated. Through the use of inert preparations (placebos), it is possible to determine if and to what extent an illness responds to placebo treatment. Needless to say, the patient should not be told that he is receiving a placebo (blind experiment). In addition, the results of therapy are dependent upon whether the physician is optimistic or pessimistic in giving the placebo to the patient. Only the introduction of a "double blind" experiment in which neither the patient, the physician, nor the hospital staff is informed as to whether a placebo or a drug is administered yields unequivocable results concerning the pharmacological activity of compounds that exceeds possible suggestive effects.

In some cases, in which objective measurement of the state of the disease is possible, a single-blind experiment may be sufficient. In any event, a statistical evaluation of the experimental results is necessary. Should the experimental design be fundamentally incorrect, the statistics can yield no useful results (e.g., by the use of noncomparable control and experimental groups). Even a double-blind experiment allows for no useful evaluation if the experimental design is poor. The use of placebos is only permitted if no better therapy is known. In life-threatening diseases, the compound to be examined must be compared only with the best of the previously used drugs in this group. However, even this approach can only be defended if other investigations have shown that the new drug is not less efficacious than those drugs already available.

The administration of placebos can result in improvement or recovery. The number of such successes is dependent upon the nature of the disease, the personality of the patient, and the physician's power of suggestion. Placebos fulfill an important role in medicine but should be used only under two conditions: (1) if true drug therapy is impossible, and (2) if the physician is prepared to conduct psychotherapy with the help of a placebo. The prescription becomes a ritual, the drug acquires the function of a talisman. Many available drug preparations are placebos. Nevertheless (or because?), they are frequently used. Basically there is no objection to prescribing a placebo as long as the above restrictions are kept in mind. In such a case it should be a completely indifferent material having no pharmacological side effects. From this point of view, homeopathic agents are acceptable since they have no principal or side effects, are prescribed in a strongly suggestive manner, and received with particular expectation.

The administration of placebos occasions not only favorable changes in psychic and bodily functions but also unfavorable ones. Numerous investigations have shown that after the administration of placebos side effects occur which have also been reported frequently as disturbing symptoms following drug administration. Thus in one series of observations dry mouth, nausea, difficulty in concentrating, sleepiness, and headache occurred in 10–25% of the cases and in 50%, a feeling of dullness. The frequency of observed side effects is dependent upon whether the patient is questioned concerning side effects and how such an interrogation is

carried out. On the basis of such observations it appears that many side effects are the result of psychic alteration intimately connected to the therapeutic process itself. In addition to the physician's questioning, expectation, mistrust, and introspection are important factors. In addition, certain reflexes may be involved.

Combined Preparations

The combination of different drugs is sometimes justified, as in the treatment of myocardial insufficiency or tuberculosis. Even in these cases, however, one should avoid prescribing a preparation with a fixed ratio of the doses of two or even more compounds. Most commercially available combination preparations do not offer any particular advantage. On the other hand, a number of disadvantages should be taken into account.

1. The duration of action of the components is unequal.
2. Mutual interaction may induce unpredictable changes in pharmacokinetic behavior (metabolic degradation, elimination).
3. The initial equilibrium between the effects of the components may be disturbed by enzyme induction during the course of therapy.
4. It is impossible to establish differences in the therapeutic effect between two, three, or even more components, or it may be impossible to clarify which of the several components is responsible for an observed effect.
5. The danger of toxic or allergic effects, unpredictable before the beginning of therapy, increases as the number of constituents rises.

It is entirely wrong to believe that one simply needs to add the effects of the individual components to obtain the desired activity, hoping that the unwanted side effects will be limited. Increasing knowledge of the mutual interaction between drugs justifies the fear of new surprises in the future. Since genetic differences exist not only for the actions, side effects, and elimination of the single components, but also for their mutual interaction, it is impossible to predict what will happen in individual cases if a combined preparation of three or more constituents is administered.

A combination preparation with two or more contituents seems completely senseless from a rational point of view. At present, hundreds of such combinations are commercially available. (For combination therapy with antiinfectious agents, see p. 269).

General Considerations on Side Effects and Drug Toxicity

Practically all drugs produce not only the expected therapeutic effect but also a series of generally undesirable effects, the so-called side effects. These side effects do not have to be necessarily undesirable. For example, the sedative side effects of some antihistamines can be useful. A new primary activity can be produced from such a side effect, such as that which

the neuroplegics of the phenothiazine group, which originally were only used as antihistamines. In the same way, the decrease in blood sugar levels produced by some sulfonamides initially regarded as a side effect was further developed to give the desired therapeutic response with the oral antidiabetics of the sulfonylurea group.

Toxic Side Effects with the Same Specific Symptoms in Every Case of Overdosage

This type of side effect is characterized by the fact that if the dose chosen is sufficiently high, every individual will suffer certain types of damage. Thus, the antibiotics, streptomycin or kanamycin, produce ear damage and complete deafness in every patient. However, the dose at which such toxicity appears in each individual is different from case to case and is not predictable. Such individual differential tolerance toward toxic effects is true of all compounds, and an individual can have a low tolerance toward one particular compound and high tolerance toward another.

The variation in tolerance between individuals is an expression of biological variation. In practically every case the causes have not been explained. Differences in uptake, distribution, and excretion, and in particular, drug inactivation can be of importance. Enzyme activities, for example in the liver, can be different in different constitutional or genetic groups; they can be changed by pretreatment with the same or another compound or by simultaneous treatment with another drug or by illness. What is true of the origins of biological variation with regard to the main therapeutic effects applies also to the side effects. It should therefore be expected that a certain proportion of patients will exhibit signs of intolerance, even if no apparent deviation from the norm appears to be present. An example of genetically determined diminished tolerance (i.e., appearance of symptoms which would otherwise be observed with overdosage) is "succinylcholine apnea" which results from a deficiency in pseudocholinesterase. The reverse situation is also possible, namely, a genetically determined increase in tolerance (e.g., coumarin derivatives). While these examples are relatively rare, there are genetically determined mechanisms which are divided approximately in the ratio of 1:1 within the population. For example, isoniazid is rapidly inactivated by about one-half of all patients, while the other half inactivate it slowly. There is no gradual transition between these two groups, but rather there exist two separate normal distributions. In pharmacogenetics, a new scientific branch, drugs are used as tools to elucidate genetic differences on the basis of the differential responses of the organism to the drug.

Idiosyncrasy

Frequently, idiosyncrasy is erroneously equated with allergy. In contrast to allergy, it is not the result of an antigen-antibody reaction, but, as the name suggests, a "peculiarity of the mixture of drug and body constituents." As a result, a reaction to certain compounds occurs with first contact and not following sensi-

tization as is true of allergy. In addition, the toxic symptoms of idiosyncrasy differentiate themselves from those of allergic reactions. The origin of such an idiosyncratic reaction is usually to be sought in an enzyme deficiency.

An example of such an idiosyncrasy having a genetic base is the occurrence of severe intravascular hemolysis in otherwise completely healthy individuals following use of the antimalarial drug primaquine. This anomaly, which was first observed in some Negroes, is also found among the inhabitants of Mediterranean countries, such as Sardinia, Italy, Greece, Israel, as well as Iran, India, and the Philippine Islands. In addition, these individuals have a hemolytic response not only to primaquine, but also to the other antimalarial drugs, pamaquine and quinacrine, as well as nitrofurantoin, phenacetin, some sulfonamides, and naphthalene. The ingestion of the fava bean and some types of green peas produces the same phenomenon, which has been known for some time as favism. In all of these cases, biochemical anomalies in erythrocyte metabolism can be measured (decrease in the glutathione content and the glucose-6-phosphate dehydrogenase activity).

Enzyme Deficiencies in Newborn and Premature Infants

Severe toxic symptoms and death have occurred in newborn and premature babies following chloramphenicol and sulfonamide (especially sulfisoxazole) as the result of an ontogenetic enzyme deficiency. Clinically, the so-called "gray syndrome" was observed following chloramphenicol with lethal cardiac and circulatory collapse. In comparable cases there was no particular increase in mortality with treatment with oxytetracycline. The high toxicity of chloramphenicol in the newborn is the result of retarded excretion of this compound in the urine. The biological half-time of chloramphenicol (i.e., the time required for the serum concentration to fall to one half of its initial value) is about 26 hr in the newborn as opposed to 4 hr in adults. Premature infants excrete chloramphenicol even more slowly. This phenomena has the following cause: in adults chloramphenicol is excreted in part unchanged and in part conjugated to glucuronic acid. The conjugated compound is much less toxic and is filtered by the glomerulus as well as being secreted by the renal tubule. In young infants the glomerular filtration rate is only about 30–50% of the adult value. Thus, it is understandable that the glomerular excretion of chloramphenicol is reduced in infants. In adults, such a reduction in the rate of glomerular filtration would not result in a diminished rate of excretion because it would be more than compensated for by the secretory excretion of conjugated chloramphenicol. The conjugation to glucuronic acid is limited to a great extent in the infant. This deficiency can be explained by the considerably lower activity of glucuronic acid transferase activity in the liver of newborn infants. This enzyme transfers the active form of glucuronic acid (uridine diphosphateglucuronic acid) to form a glycosidic bond with the hydroxyl group of the compound to be detoxified.

In infants which died following the administration of sulfonamides, especially after sulfisoxazole treatment, kernicterus was frequently observed. Because of the insufficient amount of glucuronic acid transferase in the liver, only a small amount of direct reacting bilirubin

Therefore the free bilirubin increased and led to icterus neonatorum and kernicterus. Apparently, the sulfonamide released an additional amount of bilirubin bound to protein so that the production of kernicterus was further favored.

Secondary Effects

The Jarisch-Herxheimer reaction is the result of the activity of endotoxins which are set free from microorganisms when they die as the result of the effects of chemotherapeutic agents and antibiotics. The reaction does not occur in the absence of infectious bacteria, and its occurrence should not lead to interruption or cessation of therapy. In cases in which a Jarisch-Herxheimer reaction with serious consequences is expected, therapy should be started with low doses (e.g., typhoid fever and in certain cases of tertiary syphilis and tuberculosis). These endotoxins can be primary toxins themselves or act as allergens and produce sensitization.

Antiinfectious drugs can produce under certain circumstances a transformation of the normal microbiological flora. Thus superinfections develop or the infectious disease may take a course different than that expected. These phenomena have particularly been observed with antibiotics such as the tetracyclines and chloramphenicol, but are theoretically possible after chemotherapeutic agents as well.

Allergic Reactions

Numerous drugs and toxic agents can produce allergic reactions although they are not themselves proteins. An antigen-antibody reaction results. In this case the drug or toxic agent acts as a hapten which combines with an endogenous protein to form a full antigen. This process can also take place on the surface of erythrocytes and produce hemolysis or hemolytic anemia. Such a mechanism has been demonstrated for the following compounds: phenacetin, quinine, quinidine, diphenylhydantoin, *p*-aminosalicylic acid, penicillin, and α-methyldopa. A related compound can enter into the reaction in place of the primary hapten as in group allergies (e.g., chemotherapeutic sulfonamides and benzothiadiazine). The drug itself is not always the hapten, but sometimes its metabolic products are.

The following compounds can be liberated in allergic reactions: histamine, serotonin, heparin, bradykinin, and other materials with activity on smooth muscle. Sensitization occurs with every route of administration; with many compounds it occurs particularly easily upon application to the skin and mucous membranes. The severity of the allergic response is usually considerably greater after parenteral administration than following oral doses. Only with a few compounds does severe and possibly lethal anaphylactic shock occur. The symptoms resulting from an allergic reaction can appear either immediately or after 7–12 days. Immediate reaction is produced by antigen contact with circulating humoral antibody, while the delayed reaction ("tuberculin type") is mediated by tissue-fixed antibodies. Both reactions correspond in practically all cases to those which can be elicited by other

allergens (e.g., proteins, pollen), and include reactions of the skin, the mucous membrane, the hematopoietic system, fever, and arthritis, etc. Some allergic reactions which are observed relatively frequently following drugs do not occur at all or are only very seldom observed after protein antigens, for example, thrombocytopenia and agranulocytosis. However, the type of allergic manifestation is not uniformly distributed among the various drugs. While in practically all cases skin reactions can occur, damage to the hematopoietic system, the appearance of bronchial asthma, periarteritis, serum sicknesslike reactions, and anaphylactic shock are not observed with all drugs which possess allergenic properties. It should be pointed out that an allergic reaction is not necessarily produced by the active component of a drug preparation, but can occur as well because of other components in the preparation such as drug vehicle, stabilizers, and preservatives. Contaminations related to the manufacture of the drug may be the cause of allergic reactions. This is for instance the case for penicillin and asparaginase.

Sometimes it is difficult to decide if a drug reaction is the result of allergy or toxicity. Proof of an antigen-antibody reaction which is required to demonstrate an allergy is not always easy. Occasionally positive skin reactions can be detected when the drug reaction occurs in tissue other than the skin. Negative skin tests do not provide conclusive evidence. On the contrary, in some cases these tests have resulted in a severe reaction and led to lethal anaphylactic shock. For this reason it is necessary to begin such a test with a very high dilution, under some circumstances by instillation into the conjunctival sac.

The differentiation between an allergic and toxic origin of a drug reaction is not only of theoretical interest; a toxic response is dose dependent—an allergic reaction can be very severe even after very small doses. For example, while cytostatic agents always produce agranulocytosis after large doses because of the resulting toxic damage to the bone marrow, aminopyrine in special, rare cases engenders an agranulocytosis even after small doses as the result of an antigen-antibody reaction which produces agglutination of leukocytes. The agglutinated leukocytes are continuously destroyed in the lung, and the bone marrow soon becomes depleted. A nonallergic cholestatic hepatitis can also occur after methyltestosterone and other C-17-α-alkylsubstituted steroids, while following chlorpromazine and related compounds, obstructive cholestasis of the allergic type may occur.

Diseases Produced by Drugs

If a disease state is produced by a drug which often outlasts the presence of the initiating compound, one is dealing with a particular type of damage which can be called a "drug sickness." Currently such conditions are on the increase and of ever more important medical interest. Several examples are listed: production of peptic ulcers by glucocorticoids or phenylbutazone, deafness after streptomycin, fungal overgrowths of the intestine after tetracycline, severe skin diseases following sulfonamide with a long duration of action, extrapyramidal disturbances after piperazine-substituted phenothiazines, and kidney damage after neomycin. Addiction could also be classified as a drug sickness.

Drug Dependency, Habituation, Tolerance, and Addiction

Drug abuse is the employment of a drug without medical indications or in unnecessarily high amounts. A series of compounds with central nervous system activity increase the sense of well-being, eliminate feelings of depression, or even produce an euphoric state of mind. These effects are not observed to the same extent in all individuals; sometimes they only appear after particularly high doses or after long-term administration of the drug. The physician should therefore exercise restraint in the use of such drugs so as not to induce addiction. Another variant of drug abuse is the use of compounds of the cocaine or amphetamine type by athletes (or in race horses) because they are supposed to cause better performance (see also anabolic agents, p. 238).

Many people have the desire to continually ingest various compounds. Their euphoric activity is generally the incentive for such repeated use. Frequently the result is drug dependence. Not only commonly used compounds such as alcohol, nicotine, and caffeine are involved, but also numerous analgesics, hypnotics, and other psychoactive agents. The urge to take such drugs can achieve various degrees of intensity. One is psychological dependence or habituation. In many cases the individual is capable at any time of ceasing his drug intake without harm, even if such discontinuance is accompanied by certain psychological difficulties. In other cases it is no longer possible to interrupt drug administration without coercion from the outside since the withdrawal can lead to severe symptomatology or even death. The metabolism of such an individual is completely adjusted to the constant presence of the drug. For practical reasons, both of these conditions are separated one from the other, although the transition between the two is continuous. In the first case one speaks of psychological dependence or habituation and in the second case of physical dependence and addiction.

Drug Dependency

Because of the continuous transition between habituation and addiction, the World Health Organization maintains that the more comprehensive term "drug dependence" is more suitable. The following types of drug dependency are differentiated: morphine, barbiturate, cocaine, amphetamine, cannabis (marihuana) and hallucinogenlike (LSD) types. The tendency to increase the dose, the physical dependence and the appearance of withdrawal symptoms vary among these groups; thus, withdrawal symptoms are not seen with the amphetamine and cannabis type. Alcohol dependency corresponds most closely to the barbiturate type.

Drug habituation (psychological dependence) is a condition which arises from the repeated administration of a drug. Its characteristics include

1. A desire (but not a compulsion) to continuously take a drug in order to achieve the feeling of increased well-being caused by the medication.
2. Very little or no inclination to increase the dose.
3. A certain degree of psychological dependence upon the effects of the drug, but no physical dependence and as a result there are no withdrawal symptoms.
4. Deleterious effects, if any, are exerted upon the individual.

Addiction (physical dependence) is a condition of periodic or chronic intoxication produced by repeated administration of a drug. It is characterized by

1. An overwhelming desire or genuine compulsion to continue to take the drug and to use any means available to obtain a supply.
2. A tendency to increase the dose.
3. A psychological, and a physical dependence upon the effects of the drug, which produce somatic withdrawal symptoms upon interruption of drug administration.
4. A deleterious effect upon the individual and society.

Despite the use of some compounds for many years, no addiction in the strict sense of the word results, for example, in the abuse of caffeine-containing beverages and excessive cigarette smoking. Nevertheless, in rare cases withdrawal symptoms can occur which manifest themselves somatically. Alcohol habituation which has existed for years may suddenly produce addiction after an increase in the dose (which cannot always be proved). The same is true for addictions resulting from the abuse of hypnotics and analgesics. Often the desired euphoric effects are first noted with a combination of various compounds, for example, after caffeine and barbiturates.

Habituation must be distinguished from an increase in tolerance. An increase in tolerance means that with repeated administration the dose must be increased in order to achieve a certain effect (cf. also enzyme induction, pp. 164, 325). Another use of the term "tolerance" describes the sensitivity of an organism to a particular compound.

The Therapeutic Risk

Among compounds with potent pharmacological activity there are none which are free of undesirable side effects. Neither is such to be expected from those drugs which are likely to be introduced into therapy in the future. Again and again severe and even lethal side effects have occurred only months after the introduction of a new drug. For each newly introduced drug, the physician must be informed of the possible symptoms and frequency of side effects. The physician is in a completely false position if he takes the risk of dangerous side effects in treating a trifling illness. Of course, it would be equally false to fail to use a particular drug therapy or to carry it out with insufficient doses out of fear of possible side effects if this would produce adverse effects or even death for the patient. In every case it is necessary to very carefully weigh the risk of the disease process against the risk of drug therapy.

CHAPTER 11

TOXICITY

Toxicology is appropriately divided into several areas although sharp boundaries between them do not exist.

1. The toxicology of drugs is concerned with the side effects of pharmacologically useful agents. This area is particularly important for the practicing physician. We have given the proper attention to such side effects in the discussion of the corresponding drugs. Therefore in this chapter drug poisoning will not be further considered.

2. Industrial toxicology is a separate discipline linked with industrial hygiene and medicine. Detailed discussions of the various problems involved would go beyond the scope of this book, and special monographs should be consulted.

3. The third area is toxicology of the modern environment. Man has had contact with poisons since earliest history, primarily through the ingestion of plant and animal poisons. The dangers to which man is currently exposed have become extraordinarily larger and are likely to continually grow in complexity because of the inexorable progress of our technologically oriented civilization and the increasing impingement of chemistry and technology upon daily life. The increasing pollution of the atmosphere, the rivers, and the seas has reached a degree menacing the health of mankind. The danger not only involves inhabitants of industrial regions but also people in remote areas. Heavy metals, solvents, waste gases, pesticides, food and drink, and many other types of compounds can be toxic agents. Poisoning is of greater importance in medical practice, if only because of the large number of cases. They often require specific therapy with a particular antidote and can present a problem in differential diagnosis.

General Guidelines for the Treatment of Toxic Symptoms

Measures to Prevent Absorption

Emptying of the stomach by gastric lavage or pumping is permissible if the danger of aspiration or perforation of the stomach wall can be avoided. If there is loss of consciousness, gastric lavage should be carried out only in cases in which tracheal intubation has been performed. If the technical means for lavage are not available, one can attempt to produce vomiting by the administration of warm salt solutions, as long as the victim has not lost consciousness. Adsorbants or antidotes can be added to the lavage fluid. A central emetic agent such as apomorphine (5–10 mg subcutaneously) should be avoided as far as possible because of the tendency toward collapse; it is completely contraindicated in small children.

An increase in the rate at which the contents are passed through the intestine is achieved by the administration of large doses of potent and rapidly acting laxatives. For this purpose, magnesium sulfate or sodium sulfate (20–30 gm with large amounts of water) are suitable.

The adsorption of orally ingested poisons on materials with a large surface-active area is frequently very useful. Activated charcoal (10–50 gm in 5–10% suspension) is particularly suitable for this purpose. Kaolin adsorbs less strongly (50–100 gm suspended in water).

The absorption of fat-soluble poisons can be diminished by the oral administration of nonabsorbable fat solvents. Liquid paraffin (100–300 ml) is suitable and dissolves simple halogenated hydrocarbons.

The administration of a chemical antidote can render the poisons in the gastrointestinal tract nontoxic. This can include chemical neutralization as in the administration of acids (acetic or citric acid) for alkali poisoning or alkali (magnesia or lime water, not sodium bicarbonate) in acid poisoning. Other examples of the use of a chemical antidote are the administration of sulfate ions (in the form of magnesium or sodium sulfate) for intoxication with water-soluble barium salts in order to form insoluble barium sulfate, or the administration of sodium thiosulfate in poisoning with elementary iodine (tincture of iodine) for the reduction of iodine to iodide anion.

With parenteral administration of the poison (snake bite, insect bite), the application of a tourniquet may prevent the toxic materials from reaching the general circulation and producing toxic effects.

Measures to Increase the Rate of Elimination of Poisons

A simple procedure to promote the renal excretion of many poisons is to produce a forced osmotic diuresis. An infusion of mannitol is most suitable for this purpose (cf. p. 99). An exchange transfusion is the most rapid and most effective method. The use of an artificial kidney or, less successfully, peritoneal dialysis, in order to remove part of the poison from the bloodstream can be life-saving. In such ways

patients have been saved who had ingested quantities of barbiturates and salicylates, etc., which otherwise would have been lethal.

Detoxification of Poisons Taken Up into the Body

It is possible to chemically change certain poisons so that they are no longer toxic. Examples are the binding of heavy metals by dimercaprol or ethylenediaminetetraacetic acid (chemical antagonism).

More frequently the possibility exists of diminishing the effects of the poison by a specific or functional antidote. Competitive antagonism between two compounds at the same receptor is exhibited, for example, in morphine intoxication with the administration of nalorphine, in acetylcholine intoxication with the administration of atropine, etc. Examples of a functional antidote are norepinephrine for hypotension in histamine shock, or diphenylhydantoin for cardiac glycoside toxicity on the heart. More detailed information on types of antagonism is given on page 314.

Symptomatic Treatment

One cannot discuss all the possibilities for symptomatic treatment here. Some things to be considered include: control of the circulation, blood vessel permeability, respiration, water and electrolyte balance, body temperature, the function of the central and autonomic nervous systems, therapy of pulmonary edema, etc. Depending upon the clinical picture, there is a series of symptomatic measures which when carefully carried out considerably increase the chance of survival of a poisoned individual.

Gases

Oxygen

The inhalation of pure oxygen is not as innocuous or even as valuable as had long been assumed. The inhalation of 90% oxygen by man can lead to bronchitis, respiratory difficulties with decreased vital capacity, tachycardia, and severe vomiting, as well as vertigo, paraesthesia, and other central nervous system symptoms within 24–60 hr. No such difficulties are noted after inhalation of shorter duration or continuous administration of 50% oxygen. Premature infants must not be given pure oxygen, but only a 40% enriched mixture since otherwise rentrolental fibroplasia develops.

In chronic respiratory acidosis as it occurs in emphysema with chronic hypoxemia, the respiratory center is no longer sufficiently sensitive to carbon dioxide. Respiration in these cases is primarily maintained with impulses from the carotid body which is stimulated by the hypoxemia. If this stimulation is abolished as the result of the alleviation of hypoxemia by oxygen administration, respiration is considerably

diminished. Carbon dioxide intoxication occurs which can lead to numerous central disturbances and loss of consciousness. These symptoms disappear with spontaneous or artificial respiration with air.

Carbon Monoxide

Carbon monoxide is a colorless, odorless, and nonirritant gas. It is produced from the incomplete combustion of organic compounds (including gasoline in internal combustion engines). Poisoning is frequently encountered with coal gas which may contain 5–15% carbon monoxide, and in automobile exhaust gases which contain 4–10% carbon monoxide. Poorly ventilated coal, oil, or gas ovens can produce intoxication. Large amounts of carbon monoxide are formed during blasting operations and explosions.

Mechanism of Action

Carbon monoxide is bound in the same molar ratio as oxygen to the iron of hemoglobin; carboxyhemoglobin is produced; 1 gm of hemoglobin binds 1.34 ml of carbon monoxide or oxygen. However, the affinity of carbon monoxide for hemoglobin is 300 times greater than the affinity of oxygen, so that relatively small concentrations of carbon monoxide in the inspired air displace oxygen from its binding to hemoglobin. On the other hand, high concentrations of oxygen result in displacement of carbon monoxide from the carbon monoxide–hemoglobin complex. It is a case of competition at the receptor; both oxygen and carbon monoxide compete for the receptor hemoglobin. If the carbon monoxide concentration in the inspired air is 1/300 of the oxygen concentration of 20%, i.e., 20/300 or approximately 0.07%, about 50% of the hemoglobin is saturated with carbon monoxide without regard to the time factor.

Symptoms of Carbon Monoxide Poisoning

No symptoms of toxicity are observed with a blood content of 10–20% carboxyhemoglobin, if the oxygen supply to the tissues is not already compromised in some way (anemia, arteriosclerosis). At 30–40% carboxyhemoglobin, headache, humming in the ears, vertigo, numbness, loss of consciousness, and dilation of the pupils occur; with 60–65%, deep coma, convulsions, and respiratory paralysis. Only the most prompt action can prevent death in this latter stage. The onset of poisoning is accelerated by an increase in the oxygen requirements as the result of muscular activity and by increased ventilation. The victim's complexion is fresh rather than cyanotic because the bright red color of carboxyhemoglobin differs only slightly from that of oxyhemoglobin. This color will persist after death.

Spectroscopically, it is difficult to differentiate between carboxyhemoglobin and oxyhemoglobin since both compounds have two characteristic absorption bands very near to one another. However, while oxyhemoglobin can be converted easily into hemoglobin, producing the characteristic absorption maxima of the latter compound, both bands of carboxyhemoglobin are maintained in the presence of a reducing agent.

In every case of carbon monoxide intoxication which has led to a loss of consciousness, the danger exists of hemorrhage and focal necrosis in the central nervous system. This localized damage, particularly in the brain stem, frequently results in the development of the Parkinsonian syndrome. In rare cases, demyelinization within the cerebrum occurs after several days or weeks which may be accompanied by psychotic symptoms and an organic syndrome. A certain improvement in the clinical symptoms is possible.

Although the important symptoms of acute toxicity can be explained by oxygen deficiency alone, there are some experimental findings that suggest that additional effects occur. For example, repeated inhalation of carbon monoxide produces changes in the thyroid gland which could not be obtained with comparable oxygen deficiency. If such findings can be confirmed, one will have to consider the possibility of detrimental effects following chronic exposure, even to low concentrations. This could be of practical importance in smokers, for example, in whose blood carboxyhemoglobin concentrations of 3–10% have been found.

Therapy of Acute Carbon Monoxide Poisoning

Speed is of primary importance because of the danger of delayed injury. The higher the oxygen pressure in the inspired air and the more rapid the ventilation, the more quickly the carbon monoxide is displaced from hemoglobin. In all cases one should make sure that the victim respires very well and therefore, artificial respiration with oxygen is in general the most important therapeutic measure. In mild cases of poisoning where the respiratory center still reacts well, the stimulating activity of carbon dioxide (5–7%) can be used for short periods of time. Centrally acting analeptics such as pentylenetetrazol or nikethamide are dangerous because they enhance an existing tendency toward convulsions. The administration of hypertonic solutions is effective in counteracting cerebral edema (cf. osmotherapy, p. 99).

Hydrogen Cyanide

Hydrogen cyanide (HCN) is a colorless liquid boiling at 26°C and highly volatile at room temperature. Inhalation of a dose of 50–60 mg can produce death in a very short time. The oral administration of corresponding amounts of cyanides, for example potassium cyanide, has the same effect. Hydrogen cyanide is liberated from the salt particularly by the action of hydrochloric acid in the stomach. Accordingly, such intoxication does not occur quite as rapidly as following inhalation of HCN itself. The poisonous activity is the result of blockade of iron-containing enzymes, in particular, cytochrome oxidase. Consequently, cellular oxygen utilization is abruptly interrupted. As a result the venous blood has the bright red color of oxyhemoglobin.

Poisoning can occur in the galvanizing industry, during the extermination of pests, in laboratories, and as the result of suicide attempts. The small amounts of HCN occurring in bitter almonds and in the stones of cherries, peaches, plums,

etc., are usually harmless. Nevertheless, about 80 bitter almonds contain the lethal dose of about 60 mg.

The toxic symptoms result from suffocation: headache, fever, cardiac palpitations, hyperpnea, mydriasis, followed by diminished respiratory volume, loss of consciousness, convulsions, and respiratory arrest; large doses may result in an apoplectic syndrome. The initial hyperpnea is the result of stimulation of the chemoreceptors of the carotid body. Whether the patient will survive is generally decided within a short time. Occasionally, death may occur after several days, even if the acute symptoms have been overcome. This is usually due to hemorrhage in the central nervous system secondary to the previous tissue anoxia.

The basis of the therapy of cyanide intoxication consists in the liberation of the trivalent iron from its combination with cyanide by supplying a large amount of ferric iron compound or another heavy metal which reacts easily with CN. The most rapid and simplest method of making trivalent iron available in the body is to convert part of the hemoglobin (divalent iron) to methemoglobin (trivalent iron) by the administration of sodium nitrite. Cyanmethemoglobin is then produced with a simultaneous liberation of the iron-containing enzymes of the respiratory chain. One can then attempt to form nontoxic thiocyanate from the cyanide by the administration of sodium thiosulfate. It is more effective to supply cobalt compounds, particularly if they are in a form that allows for their penetration into the cells. For this purpose, the "physiological" cobalt compound, hydroxycobalamin (vitamin B_{12a}) is probably the best antidote, but rarely is available in the necessary gram dosage. Of course, cyanocobalamin is inactive as an antidote since the cobalt is already saturated with cyanide. Cobalt-EDTA appears to be a useful compound (cf. p. 347).

If the patient is cyanotic, artificial respiration with oxygen is called for, if possible, since HCN can produce in addition paralysis of the respiratory center. Cardiac massage may also have to be resorted to. Any therapy has a successful prognosis only if it can be carried out immediately. With oral ingestion of cyanide, immediate gastric lavage and the administration of 300 ml of a 2% potassium permanganate solution to oxidize the HCN may be effective.

Hydrogen Sulfide

Following inhalation, this gas, which forms insoluble sulfides with heavy metals, leads to symptoms similar to those of cyanide. Its high affinity for iron acts as does cyanide to produce an inhibition of cytochrome oxidase. Circulation and respiration are rapidly damaged. In this case the generation of methemoglobin is not therapeutically effective, which restricts treatment to symptomatic measures.

Irritant Gases

It is easily understandable that a series of compounds with a local irritating or cauterizing effect, for example hydrochloric acid (HCl), not only are irritant when

in contact with the skin, but can produce severe irritation with inhalation of the vapors into the respiratory tree. In all such cases there is a chemical reaction with the cellular protein which produces gross changes. With low vapor concentrations such activity is restricted to the membrane surface of the eye, the nose, and the respiratory tree. The result is conjunctivitis, and possible keratitis, rhinitis, pharyngitis, laryngitis, bronchitis, and sometimes bronchopneumonia or pulmonary edema. Inhalation of higher concentrations results in glottal spasm or glottal edema. Initially, there is reflex cessation of respiration for a period of time, but it returns as the degree of suffocation increases, although this restoration of respiration may only be of transient nature.

Like hydrogen chloride, the following gases are also irritants: chlorine, hydrogen fluoride, a series of halogen-containing organic compounds such as bromoacetone, chloroacetone, and iodoacetone as well as arsenic derivatives such as diphenylaminechlorarsine. The latter two groups are also known as tear gases, because even in very high dilution they elicit marked eye pain and tear production.

In contrast to the previously mentioned compounds, nitrogen gases produce not only an acute irritant effect, but also lead to pulmonary edema following a latent period. This "gas" consists of a mixture of varying quantities of nitrous oxide, nitrogen dioxide, nitric acid, etc. It is present in fuming nitric acid and is produced by the combustion of celluloid, in explosions, during arc welding, etc. The danger produced by such gases is particularly great in closed spaces. Besides a central anesthetic effect which can be related to the content of nitrous oxide, there are local irritant effects upon the respiratory tree which correspond to those of the previously mentioned irritant gases. Subsequently pulmonary edema frequently develops after a symptom-free interval of many hours. In addition, as the result of the content of nitric acid, methemoglobin is produced, just as after administration of nitrites.

Phosgene inspired in lethal concentrations has no initial irritant effect. However, pulmonary edema develops after a latent period of several hours. Phosgene is produced in the presence of open flames from chloroform or carbon tetrachloride which may be contained in some fire extinguishers.

Ozone elicits irritant effects in the respiratory tree, bronchitis, dyspnea, severe headaches, dizziness, and fever. Pulmonary edema can develop. Marked retrosternal pain in combination with the other symptoms can simulate pneumonia or a myocardial infarction.

Inhalation of ammonia vapors can cause symptoms similar to those produced by acids. The danger is even greater since ammonia can readily penetrate into tissues because of its high lipid solubility.

Toxic Agents Forming Methemoglobin

Some poisons or drugs result in the oxidation of the divalent iron of hemoglobin to the trivalent state. The methemoglobin formed, ferrihemoglobin, is no longer capable of reversibly binding oxygen. If a large fraction of the hemoglobin is converted, symptoms of suffocation result. Individuals with methemoglobin-

containing blood appear cyanotic. Methemoglobin has a brown color *in vitro* and the spectrum shows an absorption band in the red region. Following removal of the deleterious compound, methemoglobin is again reduced to hemoglobin by the appropriate enzymes (diaphorase and reductase); however, this process is prolonged over several hours or days. The presence of small amounts of methemoglobin in the blood is generally harmless.

Along with a series of drugs (nitrites used for angina pectoris, ethylaminobenzoate, primaquine, etc.), the most common compounds causing methemoglobin anemia are nitrites, aniline derivatives, and nitrobenzene. Nitrite is added to meat products as a color preservative. Aniline and nitrobenzene are converted in the body into nitrosobenzene, the actual compound responsible for methemoglobin formation. Infants are particularly sensitive to poisons of this type because of a deficiency in the enzymes responsible for methemoglobin reduction.

Therapy

There is acute danger to life only if a considerable proportion of the hemoglobin has been converted into methemoglobin. In such cases an exchange transfusion must be performed. In no event should phlebotomy be attempted since this would result in a further diminution in the amount of available hemoglobin. In addition, the reduction of methemoglobin can be accelerated by the administration of methylene blue. Doses of 1–2 mg/kg are injected intravenously, if necessary, at intervals of 10 min. Methylene blue is more effective in methemoglobin anemia induced by toxic agents than is ascorbic acid which in turn is more active against the idiopathic formation of methemoglobin. Ascorbic acid is given in daily doses of 1 gm by mouth or intravenously as the sodium salt.

Heavy Metals

Although formerly heavy metals were frequently used in medicine, with a few exceptions (iron), they no longer are of particular therapeutic importance. However, in many cases they act as toxic compounds which cause characteristic injury. Of importance for the toxic effects is the tendency of metals to form complexes with protein in which they are particularly reactive with sulfhydryl groups. Thus, even in low concentrations metal compounds can inhibit enzymes.

The toxic effects resulting from the absorption of heavy metals are primarily observed on the capillaries. The resulting capillary damage in turn results in damage to the gastrointestinal tract (cholic and diarrhea). Simultaneously, stomatitis may occur; in the case of mercury, lead, and bismuth, a gingival "lead line" can result from the formation of the corresponding sulfide. The liver and kidneys can also be severely damaged. The high concentrations of metals in these organs as well as in the intestine are therefore of importance. Mercury, bismuth, and uranium are concentrated particularly in the

liver; and lead in the bones. There is a remarkable tendency for such metals to be stored in tissue depots from which they are released for many months, even after their intake has been interrupted.

Antidotes in Metal Poisoning

In most cases of poisoning, chemical detoxification within the gastrointestinal tract is possible. However following absorption of heavy metals only symptomatic therapy would be possible except for the fact that truly specific antidotes are available for metal poisoning. The first compound of this type was dimercaprol (2,3-dimercapto-1-propanol).

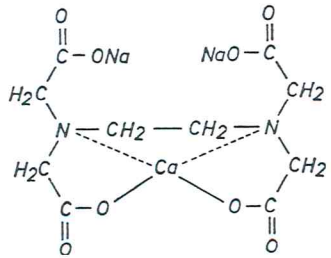
Dimercaprol is also called BAL, British Antilewisite, because it was originally developed in Great Britain during World War II as an antidote against the chemical warfare vesicant, lewisite, which is an organic compound of arsenic.

Dimercaprol *Alkyl arsenoxide* *Stable, cyclic reaction product of trivalent arsenic*

The detoxifying action of dimercaprol surpasses that of cysteine and other monothiols because a stable ring structure is formed with the metal. In this way, this compound is capable of preventing toxic metal compounds from reacting with important enzymes. In addition, the metal in the form of the dimercaprol complex is excreted in increased amounts.

Dimercaprol is effective in the following intoxications: arsenic, mercury, gold, and chromium, as well as bismuth and antimony. It is inactive or injurious in intoxications with lead, thallium, silver, selenium, and iron.

Dimercaprol is rapidly destroyed in the body. The observation that its toxicity is greater in cases of liver damage indicates that it is degraded in this organ. Side effects with therapeutic doses are generally slight. Increase in blood pressure, weakness, paresthesia, depression, nausea, and vomiting can occur.



Calcium disodium edetate

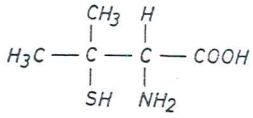
Calcium-disodium edetate is a complex salt of ethylenediaminetetraacetic acid (EDTA).

EDTA forms chelates with some metals and consequently they lose their cationic properties. Since the stability of the chelate varies with the cation, one metal can displace another if it can form a more stable chelate, i.e., if it possesses a greater affinity to the complexing agent. Calcium EDTA-sodium is particularly suitable for the therapy of lead poisoning.

Not more than 0.5 gm in about 200 ml of physiological saline is infused intravenously over 2 hr. Repetition every 8–12 hr for as long as 5 days may be necessary. Cases of death have been reported after daily doses of 2 and more grams because of anuria resulting from necrosis of the tubular cells. EDTA therapy is contraindicated with preexistent kidney damage.

Deferoxamine is a weak base obtained from various actinomycetes having a molecular weight of 561 and consisting of 1 mole of acetic acid, 2 moles of succinic acid, and 3 moles of 1-amino-5-hydroxyaminopentane. The alternating orientation of the three hydroxamic acid groups allows the compound to bind iron. Daily doses of 800 mg intravenously administered for months if necessary, increase under normal conditions the excretion of iron, particularly in idiopathic hemochromatosis. It is less effective in secondary hemochromatosis. Simultaneous oral administration diminishes enteral iron absorption. It is suitable for the therapy of acute iron poisoning.

D-Penicillamine with long-term administration produces increased excretion of copper in cases of Wilson's disease. It has a series of serious side effects, some of which are reminiscent of vitamin B_6 deficiency, although they are all caused by the loss of essential trace elements. Chronic disturbances of taste have been reported.



Penicillamine
D-3-Mercaptovaline

Specific Metal Poisons

Lead

There are numerous opportunities in our industrial society for the ingestion of small amounts of lead. Since even the daily administration of 1 mg by mouth can elicit toxic symptoms after some time, particular caution is required with persons exposed to the metal. Since some important pigments for paint contain lead (red lead, white lead, chromium yellow), painters are in particular danger as well as typesetters, those involved in the manufacture of storage batteries, foundry workers, etc. Tetraethyllead, which is added to gasoline as an antiknock agent, is absorbed percutaneously as the result of its good lipid solubility and elicits primarily anesthetic and excitatory symptoms. However, the damage occurring with the ingestion of lead-containing gasolines is primarily the result of the gasoline itself.

The lead produced by the combustion of such gasoline in engines can lead to symptoms of intoxication typical of inorganic lead in workers exposed to it. The continual increase in the amount of such combustion produced lead residues in the larger cities has continued to a threatening extent. Lead enters the body either by inhalation of lead-containing dust or by way of the mouth and gastrointestinal tract. Absorption is also possible from wound surfaces and even from the skin. The use of lead salts in astringent solutions or ointments is not recommended.

The blood level in healthy individuals is about 0.2–0.6 mg per liter. If this value increases to over 1 mg per liter, the symptoms of lead intoxication should be expected. Normally, lead is excreted in daily amounts of about 0.25 mg primarily in the feces, and to a smaller extent in the urine. In lead intoxication, the quantity found in the urine increases until it is at least tenfold greater than the normal daily amount (0.05–0.1 mg).

Lead is deposited in those places where calcium is found in the body. Thus, over 90% of lead retained in the body is deposited in the bones. The release from these depots can be prolonged over weeks and months.

Symptoms of Lead Poisoning

Acute poisoning is seldom observed. It occurs after a massive intake of lead compounds. In such cases gastrointestinal symptoms, a rapidly occurring anemia, toxic damage to the liver and kidney as well as the central nervous system are observed. Menorrhagia and abortions first occur with severe intoxication. Initially, chronic toxicity frequently produces noncharacteristic symptoms such as fatigue, headache, loss of appetite, constipation, and pallor. This pale-gray, yellow skin color called "lead pallor" is the result of the simultaneous appearance of a subicteric coloring, anemia, porphyrinemia, and spasm of the cutaneous vessels. An important symptom in most cases is a basophilic stippling of more than 0.1% of the erythrocytes. However, this can also occur in other diseases and may be absent in chronic lead poisoning. The disturbance in hematopoietic function is expressed not only by the anemia, but also by an inhibition of the enzymes involved in porphyrin synthesis. Consequently, larger amounts of coproporphyrin III and δ-aminolevulinic acid are found in the urine of patients with lead poisoning. In the erythrocytes the concentration of free protoporphyrin is increased. Apart from the determination of δ-aminolevulinic acid in the urine, the quantitative determination of δ-aminolevulinic acid dehydratase activity in the erythrocytes is of particular diagnostic importance. Attention should be paid to the occurrence of a lead line. This is a dark coloring along the edge of the gums due to the local deposition of lead sulfide. Mercury and bismuth can also produce such a "line."

Spastic constipation occurs frequently. In addition, severe painful spasms of the small intestine suddenly take place, i.e., lead colic. The attack sometimes lasts for several hours and can be accompanied by vomiting. The blood pressure is elevated as the result of vascular spasms and the heart frequency is slowed. In chronic lead poisoning, renal atrophy can develop as the result of damage to the small renal vessels. Vascular spasms also occur in many other areas, particularly the cerebral vessels. This results in increased excitability, mental confusion, with possible

hallucinations, convulsions, coma, and sometimes death in 1–2 days. This syndrome is known as lead encephalopathy. If such an episode is overcome, or even in its absence, atrophy of the optic nerve as the result of spasms of the retinal vasculature can appear. The paralysis occurring with chronic lead intoxication involves primarily the extensors of the most active muscle groups, above all those of the forearm, wrist, and fingers. The paralysis is the result of degenerative changes in the anterior horn cells and peripheral neuritis. The occurrence of chromosomal aberrations has been reported.

Therapy of Lead Poisoning

Earlier experiments to remove lead from body depots by inducing acidosis or by the administration of vitamin D did not have the expected favorable results, since the sudden flooding of the body with lead can lead to colic. The infusion of calcium disodium edetate (calcium disodium EDTA) is much more effective. This compound forms a chelate with lead, thus "deionizing" it (cf. p. 347). In this way the excretion of lead in biologically inactive form is accelerated.

In mild cases and for prophylaxis, sodium citrate can also be used. It forms a soluble complex with lead, diminishing the metal's toxic effects. Lead excretion is not more rapid. Dimercaprol is not suitable for the therapy of lead poisoning since the concentration of biologically active lead in the blood increases so markedly that the condition becomes acutely exacerbated.

Thallium

Some rat poisons contain compounds of thallium. Less than 1 gm of thallium sulfate by mouth can be lethal for man as a result of cardiac damage. The initial symptoms following ingestion are nausea and vomiting. The later symptoms are in many ways similar to those of lead poisoning, such as polyneuritis, renal damage, persistent constipation, and basophilic stippling of the erythrocytes. The complete loss of all hair is characteristic. Hormonal and psychological disturbances also take place and later an irreparable Korsakoff's syndrome may occur. Therapy can be attempted shortly after the intake of thallium with activated charcoal and sodium sulfate. Dimercaprol and Ca-EDTA are ineffective.

Mercury

Mercury and compounds of mercury earlier played an important role in medicine. One need only remember the treatment of syphilis with mercuric ointment or disinfection with corrosive sublimate (mercuric chloride, $HgCl_2$). Industrial intoxication with mercury may occur in part as the result of the intake of mercury in the vapor form. All individuals are in danger who work in rooms in which uncovered metallic mercury is found; for example, in chemical and physical laboratories, or with the manufacture of barometers and thermometers.

Acute poisoning is usually caused by the corrosive sublimate. The compound is markedly corrosive and therefore produces severe vomiting following oral intake. Salts of mercury produce a liquefying necrosis and are readily absorbed. Be-

absorption of the poison, transient polyuria occurs, followed by oliguria or anuria as the result of necrotic damage to the renal tubules. Death usually results within a week. Considerable amounts of protein, erythrocytes, and casts are found in the urine. In addition, in the course of hours or days, a mucomembranous colitis develops with severe, bloody diarrhea. This damage can also result in death, particularly in cases with less pronounced kidney damage. If the anuria is survived, it is usually followed by a stage of polyuria.

In subacute intoxication, changes in the oral cavity are also seen. Along with increased salivation, there is "mercurial stomatitis" with inflamed and ulcerative changes in the mucous membranes, particularly at the edge of the gums. With cases of longer duration, the deposition of mercuric sulfide causes a dark line to appear at the edge of the gums. Damage to the kidneys and the intestines can occur in such cases just as with acute intoxication.

In chronic intoxication, stomatitis can also be observed, but the predominant symptoms are related to brain damage. That this organ is a preferred site of toxicity is related to the uptake of mercury in the vapor phase through the mucous membranes of the nose. The poison is transported from there by the lymphatics along the olfactory nerves to the anterior portion of the brain. Patients exhibit nervous unrest, irritability, inability to concentrate, insomnia, as well as an intention tremor. Patients become cachectic with further progress of the intoxication. Lipid soluble alkylmercury compounds (such as ethyl- and methylmercury) accumulate in the central nervous system; such is the case with oral administration as well. These compounds are found in industrial waste water, and in addition, are produced from inorganic mercury salts in the environment (e.g., in fish). Alkylmercury compounds elicit primarily very severe neurological symptomatology including possible psychosis. The condition lasts for a long time because of the very slow rate of elimination of the toxic agent.

A short stay in a room in which only small amounts of mercury are found (small droplets between the floorboards) can produce in some individuals severe swelling of the mucosa of the nose and respiratory tree. This is not a toxic effect of mercury, but the result of an allergic reaction. With such hypersensitivity, but only thereby, dental fillings with amalgam can produce unpleasant reactions. Allergic skin reactions also occur.

Therapy

Acute intoxication requires rapid measures. One should attempt to remove as much of the poison as possible by gastric lavage. Such lavage can be dangerous where there have been marked corrosive effects. In any event, sufficient amounts (40–60 gm) of activated charcoal are called for to adsorb the poison. For the detoxification of absorbed mercury, dimercaprol is very effective and almost always life-saving when promptly administered. The initial dose is 3 mg/kg every 4 hr, injected into the gluteus muscle. Later, injections are made every 6–12 hr for about 10 days. Since dimercaprol can only be given by the intramuscular route as an oily solution, and its effects are therefore not immediate, in highly acute intoxication it is useful to begin therapy with a simultaneous intravenous dose of the sulfhydryl

group-containing amino acid, cysteine. As is demonstrated in Fig. 68 in a model case, toxic effects on the heart produced by mersalyl, an obsolete mercury diuretic, are immediately alleviated. Methicillin, a semisynthetic penicillin derivative that yields a complex with mercury also seems suitable as an antidote. Concern should be given to compensating for disturbances in electrolyte and water balance. Fluids should not be given in too large quantities. Subacute and chronic intoxication can also be treated with good results with dimercaprol.

Bismuth

The toxic symptoms resulting from bismuth are very similar to those of mercury. Stomatitis, colitis, renal damage, and occasionally icterus and dermatitis can occur. Again, the best antidote is dimercaprol.

Gold

Poisoning is possible when gold is used for therapeutic purposes (cf. p. 145). Stomatitis, enteritis, dermatitis (possibly exfoliative), damage to the eye, icterus, agranulocytosis, panmyelophthisis, lupus erythematosus occur. Dimercaprol is capable of detoxifying gold present in the body and promoting its excretion. Otherwise, gold may be retained for months or years.

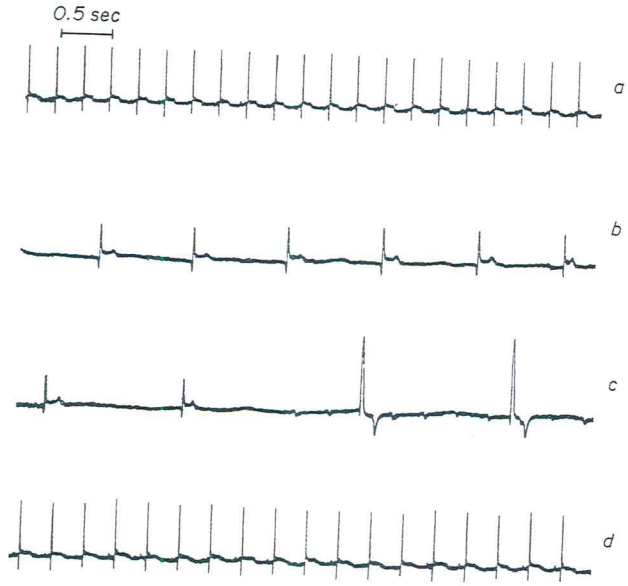


Fig. 68. EKG of an anesthetized guinea pig. Intravenous infusion of an organic mercury compound (mersalyl 42 mg/kg in 7 min). Subsequent injection of cysteine (53 mg/kg). (a) EKG prior to mersalyl infusion. (b) After the infusion. (c) Beginning of the cysteine injection. (d) Immediately following cysteine administration. Note the complete abolition of the signs of mercury intoxication.

Arsenic

Arsenicals previously were widely used in medicine (arsenic trioxide, arsphenamine, and related chemotherapeutic agents). Arsenic trioxide (As_2O_3, anhydride of meta-arsenous acid) has no primary local effect. After 1–2 days of contact with tissue there is damage to the capillaries with stasis and thrombosis concluding with circumscribed necrosis at the point of contact. In the absence of capillaries, arsenic has no necrotic effect, as shown by its lack of activity upon application to the cornea.

The acute toxic or lethal effects of arsenic after oral or parenteral administration are also related to the poison's effect upon the capillaries, resulting in the following symptoms: severe gastroenteritis with vomiting and rice-waterlike stools (gastrointestinal form) followed by hemoconcentration, disturbances in the electrolyte balance, and circulatory failure. The "paralytic form" of acute intoxication is observed less often and only following very large doses. The consequences are general weakness, loss of consciousness, coma, and death with vasomotor and respiratory paralysis.

With chronic intoxication, one frequently finds hyperkeratosis and sometimes skin hyperpigmentation (melanosis) and changes in the nails. Inflammation of the mucous membrane of the eyes, the nose, the mouth, and the gastrointestinal tract as well as polyneuritis occur. Liver and bone marrow damage is less frequent. After long latent periods of 15–20 years, skin carcinoma, cirrhosis, and hepatic tumors as well as bronchial carcinoma have been observed. So-called "nickel cancer" occurring in the nose of workers in the nickel industry is also caused by arsenic.

The organic arsenicals, arsphenamine or neoarsphenamine, were formerly used very extensively for the treatment of syphilis. Other examples of this class are tryparsamide, used against African sleeping sickness and certain compounds such as carbarsone or glycobiarsol used against amebic enteritis. The toxic symptoms following these organic arsenicals are characterized by the appearance of hepatitis, exfoliative dermatitis, hemorrhagic encephalitis, and agranulocytosis. In addition, damage to the kidneys and optic nerve, and anaphylactoid and allergic reactions occur.

Analogous to mercury poisoning and with similar results the therapy of acute and chronic poisoning is accomplished with dimercaprol. The severe disturbances of water and electrolyte balance and of the circulation which occur with acute poisoning must be handled symptomatically. The symptoms of toxicity following organic arsenicals can also be successfully treated with dimercaprol.

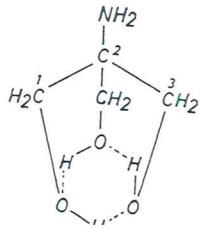
Acids

Following the intake of acid by mouth, there is local irritant or caustic activity in the mouth, throat, esophagus, and stomach. Such burns can lead to secondary pathology by acute perforation of tissues or by later infection or stricture development.

Following the absorption of acids in the gastrointestinal tract or the endogenous metabolic production of acids, for example, in diabetes mellitus or respiratory insufficiency, the following can be observed: despite the administration or production of large amounts of acid, the blood pH remains unchanged for a long time because its buffering capacity is excellent. This should mainly be attributed to hemoglobin and the plasma proteins. In addition, the phosphate and bicarbonate buffer systems are of importance. For maintenance of the pH, a constant relationship of carbon dioxide to bicarbonate (1:18) in the blood is of great importance. Carbon dioxide is liberated from bicarbonate after the administration of acids. This results in the stimulation of the respiratory center with increased respiration. Thereby the excess carbon dioxide is exhaled until the ratio of carbon dioxide to bicarbonate of 1:18 is reestablished. This process only is possible until such time as the blood bicarbonate is exhausted (alkali reserve). Only at this point does acidosis develop with a decrease in pH, while previously one speaks of a compensated acidosis. With the fall in pH the respiration is markedly slowed but increased in depth (Kussmaul respiration), the blood pressure falls, and a comatose condition develops. In acidosis the excretion of primary sodium phosphate is increased at the expense of secondary sodium phosphate. The urine is strongly acid because the secretion of H^+ ions in exchange for sodium ions in the tubular cells is increased. In addition, increased amounts of ammonium ions are formed in the distal nephron from ammonia and protons.

Therapy of acid poisoning is symptomatic in cases of local damage. Above all, gastric lavage should be avoided because of the danger of perforation. Magnesia should be used instead of sodium bicarbonate for neutralization because the latter can result in gastric ruptures as the result of the formation of carbon dioxide. Absorptive poisoning is treated with an intravenous infusion of alkali, for example, 7–8% disodium phosphate or 1.7% sodium lactate. Phosphates have a particularly beneficial effect on acid excretion by the kidney. During the last few years the administration of tris buffers (THAM) has also proved useful in such therapy. The urine must be constantly checked for the appearance of an alkaline reaction in order to avoid alkalosis. In aqueous solution tris buffers act as weak bases and combine with protons. THAM is also suitable for the treatment of acidosis of other origin, for example, in shock and burns.

The compound is relatively nontoxic, but is very slowly excreted; accumulation is therefore possible. Generally a 0.3 *M* isotonic solution (4%) with a pH value of 10.2 is infused very slowly intravenously with a maximal dose of 1.5 gm in 24 hr. Should disturbances in respiration result, mechanical ventilation and the administration of oxygen are necessary.



Tromethamine
"Tris buffer" (THAM)
Tris(hydroxymethyl)aminomethane
or
2-Amino-2-hydroxymethyl-1,3-propanediol

Some acids produce specific effects apart from the nonspecific effects due to the acid as such. Such intoxications that may be of great importance are dealt with below.

Carbon Dioxide

The inhalation of carbon dioxide in high concentrations elicits a series of symptoms which one assumes are not only related to the acidic character of the compound but also to specific effects. It is also possible that these differences are only owing to the fact that carbon dioxide permeates tissues very readily. Hyperpnea, headaches, sweating, unrest, humming in the ears, vertigo, mental confusion, and excitation can be the result. This may be followed by convulsions, or by apathy and coma.

Hydrogen Fluoride

Hydrogen fluoride has a direct cauterizing effect on tissues. As a result, damage to the pulmonary tissues can result following inhalation, just as with other irritant gases.

Hydrogen fluoride and fluoride at high dilutions inhibit a series of important enzymes. In addition, fluoride has an effect on calcium metabolism since calcium fluoride is poorly soluble. With chronic administration of fluoride there is a loss in weight, brittleness of the bones, anemia, generalized weakness, joint stiffness, and spotty discoloration of the teeth ("mottled enamel"). Since the teeth of individuals with a high intake of fluoride displayed this spotty discoloration, but rarely developed caries, the influence of fluoride administration on the frequency of caries development was systematically investigated. The conclusion was that regular intake of drinking water containing 1 mg of fluoride per liter optimally diminished the incidence of caries if it was carried out from birth to the end of dentition. Dental caries are not completely suppressed but the frequency of their occurrence is appreciably reduced. Fluoride replaced a hydroxyl group in the apatite of the teeth. This apatite is particularly resistant to acids. It is also probable that in adults, remineralization of the dental enamel occurs owing to the effects of fluoride-containing saliva. Many cities now add fluoride to their drinking water. Additional intake of fluoride is then no longer required since 1.5 mg of fluoride per liter of drinking water can result in mottled teeth. Even though this may appear to present only a cosmetic problem, if caries prophylaxis is to be carried out with fluoride-containing tablets, the fluoride content of the drinking water should be taken into account. The long-term administration of fluoride to patients with osteoporosis frequently induces the increased formation of bone material that is, however, of doubtful quality.

Oxalic acid and its salts have a specific effect because they form insoluble compounds with calcium. This results in symptoms of calcium deficiency which in acute intoxication with large doses can even be lethal if they cause tetany and

cardiac and vascular insufficiency. In protracted nonlethal intoxication, symptoms of renal insufficiency are the most prominent; they probably are the result of a blockage of the tubular lumen by oxalate crystals. Therapeutically, one must attempt to bind the oxalic acid in the gastrointestinal tract by gastric lavage with saturated solutions of calcium hydroxide. In this way the corrosive effects of the acid are also antagonized. Following the absorption of oxalic acid, parenteral calcium administration is indicated. Renal insufficiency must be combated with the usual methods. The prognosis with such therapeutic measures is generally good.

Bases

Strong bases act upon the skin and mucous membranes in a manner similar to strong acids and precipitate proteins. However, the scab is less firm so that the base can penetrate more deeply into the area of liquefying necrotic tissue. Therefore damage is generally more severe than after a comparable acid burn. This is also true of the scar formation that takes place after tissue corrosion induced by bases. There is consequently a greater danger of stricture occurrence in the esophagus than following acid-induced corrosion. Strongly alkaline solutions of drugs can provoke tissue necrosis upon subcutaneous and intraarterial injection (e.g., barbiturates) and can produce severe nerve damage after intrathecal administration (e.g., basic sulfonamide solutions). Most frequently, caustic burns occur as the result of the ingestion of potassium or sodium hydroxide or of ammonia. With the latter compound, the uptake of ammonia vapor by the lungs and its good lipid solubility result in a particularly penetrating activity.

Gastric lavage is contraindicated because of the danger of perforation. The administration of large amounts of water, if possible with the addition of weak acids (citric acid, acetic acid, etc.), is the proper treatment.

Strongly basic potassium soap solutions are sometimes injected into the uterus to illegally induce abortion. Often the result is a sudden high concentration of potassium salt in the blood that provokes severe hemolysis. There further develops an acute renal failure as the result of the blockage of the tubular lumen by hemoglobin or methemoglobin. Immediate exchange transfusions are the best therapeutic measure in severe cases. In order to maintain the hemoglobin in solution during its passage through the renal tubules, very large amounts of liquid should be given along with doses of sodium bicarbonate until the urine is weakly alkaline. Water and sodium bicarbonate administration is only indicated prior to the onset of oliguria. Oliguria or anuria must be handled in the usual way.

Organic Solvents

From year to year growing amounts of organic solvents are manufactured and used for various purposes: to dissolve fats, dyes, lacquers, plastics, rubber, glues, for extractions in the manufacture of chemicals, for use in the dry cleaning in-

dustry, etc. Poisoning is therefore increasingly common. The technical products are generally not pure so that the observed effects are not always caused by the compound for which the product is named. In addition, allergic reactions may also occur. They can be caused by the main component or some minor product.

Despite various chemical structures, all organic solvents have similar toxic effects precisely because of their good solubility in lipids. Although they generally enter the body by inhalation, uptake through the skin should also be considered (e.g., carbon tetrachloride). In such cases the same generalized intoxication can occur as after inhalation but also local, more limited tissue damage can develop, in particular to nerves. These solvents act either as depressants or stimulants on the central nervous system; the function of peripheral nerves can be damaged. Frequently, degenerative changes in the liver, kidneys, and heart are observed. Some compounds additionally damage the hematopoietic system, elevate the tendency toward bleeding, or affect the production of hormones. The depressant effect can vary all the way from dizziness, headaches, nausea, vomiting, uncertainty in gait, and a crushing sensation in the chest to deep coma and respiratory paralysis. The excitatory effects extend from mild unrest and psychic excitation to severe convulsive episodes. The symptoms of excitation and depression are frequently mixed or alternate one with the other.

Inhalation of low concentrations of some organic solvents can elicit euphoria in some individuals. It has been known for a long time that anesthetics (ether and chloroform) which in general possess activity similar to the organic solvents have been intentionally inhaled by some individuals to produce a state of intoxication. The result is a series of symptoms which are similar to those of chronic alcoholism. Euphoric effects have also been described following the inhalation of benzene, gasoline, and trichloroethylene. The practice of "glue sniffing," which is becoming increasingly frequent in the United States, should also be considered as an example of such a euphoric effect from an organic solvent. The sniffer inhales solvent vapors generated by squeezing a tube of glue into a handkerchief or paper bag. The result is not only a sense of euphoria, but also hallucinations and delusions or even possibly loss of consciousness for hours. The dose must be increased more and more with repetition. A genuine dependency develops. Acute lethal cases occurring after the inhalation of toluene, benzene, gasoline, trichloroethane, and fluorinated hydrocarbons (propulsion gases from spray cans) are no longer a rarity in the United States (cf. also p. 28).

In the following discussion the types of solvents will be listed with specific examples used in daily life as well as the symptoms which occur in addition to those named above.

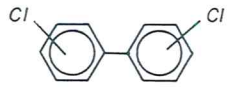
Hydrocarbons

The occurrence of a toxic aplastic anemia is characteristic of chronic gasoline and benzene poisoning. Mucous membrane hemorrhages also occur.

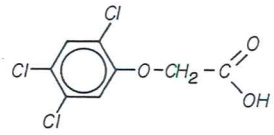
Halogenated Hydrocarbons

The "classic" compounds from this group (such as chloroform, halothane, carbon tetrachloride, tetrachloroethane) besides their effects on the central nervous system

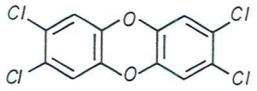
and their ability to sensitize tissues to the effects of catecholamines, also produce damage to the liver which can result in acute yellow liver atrophy. The kidneys are generally affected and the cause of death must sometimes be attributed to kidney failure. Carbon tetrachloride, in particular, is frequently involved in such intoxication. It is not only used as a solvent, but also in fire extinguishers. A series of chlorinated, aromatic compounds is continuously taken up by man and animals from the environment. They are not liable to metabolic degradation and are highly lipid soluble. Therefore, they cannot be excreted and accumulate in adipose tissue and in the central nervous system. Besides chlorophenothane (cf. p. 262), polychlorinated bisphenyl derivatives belong to this group. The latter compounds are widely distributed as plasticizers in plastics and they are dispersed in the atmosphere upon combustion of such materials. Tetrachlorodibenzo-*p*-dioxane occurs as a contaminant of herbicides of the artificial growth-promoting compound trichlorophenoxyacetic acid and is also mobilized upon combustion of herbicide-containing plants. The possibility of chronic intoxication with chlorinated aromatic compounds has already been dealt with in the discussion on chlorophenothane. In addition, it has been reported that tetrachlorodibenzo-*p*-dioxane possesses teratogenic properties even in low concentrations.



Polychlorinated Biphenyls



Herbicide Trichlorophenoxyacetic acid



2,3,7,8,-Tetrachlordibenzo-p-dioxane

Alcohols

Methanol, which is very widely used as a solvent, is much more toxic than all other alcohols because its metabolic behavior is completely different (for details cf. p. 366). The higher alcohols, in contrast to ethanol (cf. p. 363), produce considerably more unpleasant central nervous system and gastrointestinal tract symptoms.

Glycols

Ethylene glycol and propylene glycol are relatively nontoxic. Only after the administration of very large quantities does severe intoxication occur as the result of kidney damage. 1,3-Propylene glycol is two to three times as toxic as 1,2-

propylene glycol. The use of these glycols for the disinfection of air is not dangerous (cf. p. 255). Diethylene glycol and other ethers of this group are considerably more toxic. In 1937 a manufacturer in the United States prepared a sulfonamide elixir containing diethylene glycol. Numerous individuals died following the ingestion of this material as the result of kidney and central nervous system damage. Glycerin has a high affinity for water and can cause local irritation or hemolysis in the case of intravenous injection. Otherwise, glycerin is nontoxic, particularly since it can be utilized in metabolism.

Carbon Disulfide

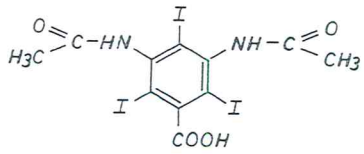
The acute anesthetic effects of carbon disulfide (CS_2) are similar to those of chloroform. With chronic industrial poisoning, manifold psychic and neurological disturbances occur as the result of degenerative processes in the brain, spinal cord, and peripheral nerves. This poison enters the body primarily through the lungs but is also capable of penetrating the skin. In the latter case local nerve damage is possible. With chronic poisoning mental acuity can be disturbed or hysteric reactions and psychosis may occur. In addition, various types of neuritis or a Parkinsonlike syndrome, gastrointestinal disturbances, and impairment of the functions of the adrenal and the reproductive organs can be observed.

X-Ray Contrast Materials

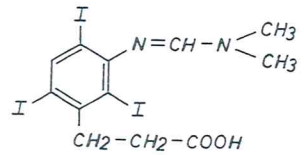
Barium sulfate is used for X-ray visualization of the gastrointestinal tract. Poisoning with this completely insoluble compound does not occur. Mistaken use of soluble barium salts has resulted in severe toxicity since barium ions produce spasms of the entire smooth musculature and damage cardiac function (cf. p. 49).

Organic compounds containing two or three iodine atoms are used as contrast agents for other organs and cavities. These compounds are either injected directly into the appropriate cavity (bronchography, hysterosalpingography, localization of fistulas and sinuses, urethography, retrograde pyelography, etc.) or into the blood vessels themselves (angiography). The contrast agent can be administered intravenously or orally for anterograde urography or for cholecystography or cholecystangiography.

Iodine-containing aminobenzoic acid derivatives are preferred for the visualization of the renal pelvis in which they give a good radiographic shadow. These compounds are relatively poorly bound to plasma protein and large amounts are filtered by the kidney. That portion secreted by the tubular cells is relatively unimportant at high plasma concentrations, but at low plasma concentrations the single passage of blood through the kidney is sufficient to completely clear these iodine-containing compounds. If one knows the concentration in the arterial blood and the amount excreted in the urine, one can calculate the renal blood flow. The binding to plasma protein is so strong with some compounds that they interfere with diagnostic tests of thyroid function for several months. Examples of such compounds are diatrizoate and for oral cholecystography, ipodate.



Diatriazoate
3,5-Diacetamido-2,4,6-triiodobenzoic acid



Ipodate
3-[(Dimethylaminomethylene)amino]-2,4,6-triiodohydrocinnamic acid

Side Effects

Although these compounds are not toxic in the usual dose, one must expect following intravenous administration allergic or even anaphylactic reactions in 6–25% of all cases. Death seldom occurs in adults if all precautions have been met. Pretreatment with an antihistamine reduces the frequency of such reactions. Mortality of more than 0.3% has been reported in angiocardiography of children with congenital heart defects. The allergic response is characterized by urticaria, palpebral and glottal edema, physical distress, retching, sneezing, coughing, bronchial asthma, circulatory collapse, coronary insufficiency, and renal failure. For treatment the usual compounds for allergic reactions can be used: calcium salts, antihistamines, intravenous prednisolone, and in cases of bronchial asthma and anaphylactic shock, theophylline and epinephrine or isoproterenol infusion.

A very small intracutaneous test dose given the previous day or 1 hr before injection may be of prophylactic value. A negative response to this test does not exclude possible lethal results; even the test dose itself has resulted in death. Oral administration is preferable when possible. These compounds are contraindicated in individuals with a tendency toward allergic reactions, with hypersensitivity to the test dose, in renal and liver insufficiency, severe cardiac and circulatory disease, acute pancreatitis, hyperthyroidism, and in iodine hypersensitivity.

Tobacco

The alkaloid nicotine contained in tobacco is a potent poison; the lethal dose is about 50 mg. It produces tonic-clonic convulsions within a short time and death as the result of respiratory paralysis. Smaller amounts have their primary effect upon the autonomic ganglia (for details cf. p. 38). Certain central excitatory effects are demonstrable.

Only about 30% of the nicotine in a cigarette or cigar is carried in the mainstream of cigarette or cigar smoke into the mouth of the smoker. The larger amount of nicotine is dispersed by the burning end directly into the surrounding air so that those present, particularly in small rooms, must also "smoke." With a cigarette containing 1 gm of tobacco and 1% nicotine, 30% (3 mg) reaches the mouth. If the smoke is puffed out without inhalation, about 5% is absorbed, whereas

moderate inhalation leads to absorption of about 70% and strong inhalation with temporary retention of the inhaled air results in 95% absorption. With the smoking of sour tobacco of a cigarette and sometimes that of pipe tobaccos, the smoke carries nicotine salts which are easily exhaled again from the mouth. For this reason the smoker must inhale to take up sufficient nicotine. The smoke of alkaline cigar tobacco contains nicotine base which can be easily absorbed from the oral cavity. Therefore, cigar smokers do not need to inhale in order to obtain a sufficiently high dose of nicotine. In the smoking of a cigar (and to a smaller extent a cigarette) vaporized nicotine is initially trapped in the last third of the cigar and carried in the smoke only when this last third is smoked. Analysis of nicotine uptake in the oral cavity has shown that the first third, second third, and remaining portion contain increasing amounts of nicotine. It is therefore important as far as nicotine uptake is concerned how far the cigar is smoked. This is also basically true of cigarettes, taking into account their different size. The rhythm and rate of smoking are also important determinants of the amount of nicotine uptake. Nevertheless, the acute lethal nicotine dose of about 50 mg cannot be achieved by smoking. Such a dose could only be taken up by smoking of 20–40 cigarettes. The time required (90–180 min) is entirely sufficient for the elimination of the nicotine taken up from the first cigarettes of such a series. About 10% of the nicotine is excreted by the kidney unchanged and 80% metabolized, primarily in the liver.

Frequently repeated administration of nicotine results in habituation. Tolerance toward the compound can be elevated two- to threefold. This increased tolerance can disappear in diseases associated with fever, organic brain damage, or severe anemia. Aside from this relatively long-term elevation in tolerance, tachyphylaxis lasting for at most 2 hr can be observed. Therefore, a cigarette has a more marked effect if it is smoked after a longer period of abstinence (e.g., in the morning, after a night's sleep).

The relationship of smoking to diseases of the heart and circulation has been frequently investigated. During smoking, acute changes in the EKG, blood vessel tone, and the bronchi are observed which can be explained by excitation of the cholinergic or adrenergic systems. Although acutely there is diminished blood flow in the skin, such reactions do not necessarily result in organic diseases of the heart and vasculature. Since the causes for the development of arteriosclerosis are manifold and the disease occurs frequently, it is difficult to demonstrate that smoking is a cause for the development of arteriosclerosis. Nevertheless it has been shown that the smoking of cigarettes (not of cigars or a pipe) carries increased risk for the development of coronary artery disease and its complications. The concentration of lipids is elevated in the plasma of heavy smokers. In patients who had recovered from a myocardial infarct, cigarette smoking diminished cardiac function, under some circumstances to the point of cardiac insufficiency.

Thromboangiitis obliterans (Buerger's disease) appears practically only in heavy smokers. Even smoking a few cigarettes can initiate the progression of the disease after it has been arrested by abstinence from smoking. Possibly, in such circumstances there is also an allergy to certain constituents of the tobacco. Other peripheral angiopathies practically never occur in nonsmokers prior to the age of 55.

to be elevated by smoking. The formation of ulcers in the stomach and duodenum is probably not promoted by smoking, but the healing process is retarded. The primary degenerative damage of the optic nerve (tobacco amblyopia) occurring in some smokers is accompanied by a reduction in the blood level of vitamin B_{12}. Smokers without disturbances in vision have normal values. Even patients suffering from pernicious anemia who are heavy smokers usually do not show any disturbances of vision.

About 500 other compounds have been identified in the mainstream of tobacco smoke along with nicotine. Some of these are of toxicological importance. They can be divided into three groups.

1. Carbon monoxide
2. Irritant gases and vapors, above all, aldehydes and ammonia
3. Tars, arsenic, and chromium as potential carcinogens (possibly also radioactive polonium^{210})

The carbon monoxide content in the mainstream of a cigarette is about 1–3%, of a pipe 2%, of a cigar about 6%. Since the amounts of carbon monoxide absorbed are small, there is no intoxication. The blood of a smoker who inhales about 20 cigarettes a day contains about 5% carboxyhemoglobin. With heavy smokers concentrations of 10–15% and even more can occur which, with strong physical exercise, heart disease, or exposure to high altitudes, could have grave consequences.

Among the irritant gases, the various aldehydes as well as ammonia are of particular importance in alkaline tobacco. They are responsible for the development of smoker's cough and for chronic bronchitis. Some constituents of the smoke inhibit ciliary movement. The frequency of upper respiratory diseases is considerably higher in smokers than in nonsmokers. This is partially responsible for the decreased life expectancy of heavy smokers.

Of the three materials known to be carcinogens on the basis of industrial toxicological experience (tars, arsenic, and chromium), tar is most likely to be responsible in the case of tobacco smoke. It is known from workers in gas plants breathing tar vapors that the incidence of death from bronchial carcinoma is increased 10 to 15-fold. The disease shows up after an exposure of 10–15 years. A similar exposure time and frequency of bronchial carcinoma should be expected in cigarette smokers. In this regard it is of interest that the potent carcinogenic substance, *o*-aminophenol, can be demonstrated in the urine of smokers. According to very thorough and critical British investigations, the mortality from lung cancer is about 30 times higher in those who smoke 40 cigarettes per day than in nonsmokers. But even with a daily consumption of 20 cigarettes, it is 15 times higher and with only 8 cigarettes 10 times higher. Data obtained in the United States show basically the same results. Pipe smokers suffer bronchial carcinoma "only" about three to four times as frequently as nonsmokers. Similar values for cigar smokers are close to those of nonsmokers or only slightly elevated. The supposition that because of the long latent period of 10 to 15 or even more years it is senseless to stop after years of smoking is not defensible since even with abstinence of less than 10 years, the frequency of lung cancer falls by about one half. Finally, a statistical correlation between

smoking and cancer of the larynx, mouth, pancreas, and bladder has been established.

Metaplastic changes of the bronchial mucous membranes which are also present in bronchial carcinomas are found in heavy smokers. This metaplasia is largely reversible with cessation of smoking. The risk of developing cancer is increased with chronic bronchitis with sputum production. Probably, several compounds act together in the development of bronchial carcinoma. Several carcinogens (e.g., benzpyrene) and cocarcinogens (e.g., phenols) are found in tobacco tar. Cocarcinogens are capable of allowing subthreshold doses of carcinogen to be active under experimental conditions.

Risk Involved in Smoking

If one considers not just lung cancer or coronary artery disease but also the influence of smoking on life expectancy in general, one obtains impressive figures. Statistics in which the smoking habit of British physicians was related to life expectancy showed the following: the chance at age 35 of dying within the next 10 years was 1:23 for heavy cigarette smokers and 1:90 for nonsmokers. Fifteen percent (1 out of 6) will die before reaching age 65 if they do not smoke; 33% (1 out of 3) if they smoke heavily. Even if the entire difference is not attributable to smoking, these figures are nevertheless useful in order to demonstrate the considerable influence that smoking has upon life expectancy.

Preventive Measures

Since the initiation of the smoking habit is primarily dependent upon social factors, one should attempt, by suitable measures, to generate antipathy toward smoking in children and young people. This is practically a hopeless undertaking as long as the cigarette industry spends millions of dollars yearly on advertising which promises well-being, compatibility, and exhibits smoking as a status symbol.

Physicians can contribute greatly toward prophylaxis if they request their patients to no longer smoke as part of the treatment for bronchitis, duodenal ulcers, or vascular disease. They will be more convincing if they themselves do not smoke. If the patient cannot or will not give up smoking, the following guidelines are important: pipe smoking or, even better yet, cigar smoking is much less damaging than cigarette smoking. The lack of inhalation and a better relationship between nicotine uptake and elimination are important in this regard. Cigars and cigarettes should be smoked only to the last third of their length. In principle, a good filter could better retain the damaging compounds. It was demonstrated that 10 years after the change from nonfilter cigarettes to filter cigarettes the risk of bronchial carcinoma was statistically diminished. Thirteen years after complete cessation of smoking the magnitude of this risk approached that of nonsmokers. However, most of the currently available filters are not better and in fact may be worse than tobacco itself, which acts as a filter.

Alcohols

Ethanol (Ethyl Alcohol)

Ethanol acts as a local irritant and results in hyperemia of the skin and mucous membranes. Acute or chronic pharyngitis and gastritis can result after long-term use. About 20% of the alcohol is absorbed from the stomach; the remainder from the small intestine. Quantitative relationships are very strongly dependent on the extent of filling of the gastrointestinal tract so that a considerable difference exists between absorption from an empty intestine and that following a rich meal.

Absorption from the oral cavity and esophagus should be expected with the drinking of concentrated alcohol in small sips. In such cases the liver is bypassed and the effect is more rapid and intense. Alcohol is detectable in the blood within a few minutes after its oral intake. The blood levels increase in 45–90 (up to 120) min to a maximal value dependent upon the amount of material in the stomach.

Alcohol distributes itself throughout the total body water following absorption. The blood alcohol level is dependent upon:

1. The amount of alcohol ingested
2. The rate of absorption, which is determined in part by the alcohol concentration (beer, 4–5%; brandy and other distillates, 30–45%; white and red wine, 7–10%; sweet wines, 15%)
3. The body weight or the quantity of body water
4. The rate of alcohol elimination

Correspondingly, the blood alcohol level cannot be predicted in individual cases, with any certainty. One liter of beer or a corresponding amount of another alcoholic beverage produces a blood alcohol concentration of 0.05% in an individual weighing 65 kg; 2 liters of beer, a level of 0.15%.

The elimination of alcohol begins immediately after its administration. The excretion of unchanged alcohol via the kidney, respired air, and skin contributes only a few percent; the remainder is metabolized. The amount of alcohol oxidized per unit time is constant. It is about 0.1 gm/kg × hour for men and 0.085 gm/kg × hour for women. These values vary by ±30% from individual to individual while they remain rather constant within a given individual. In a corresponding way one can expect a uniform fall in the blood alcohol concentrations within an individual. These values decrease by 0.01–0.02% per hour; generally about 0.015%. Thus, the fall in blood alcohol is *linear* with time. Such behavior represents an extreme exception. Usually, compounds are eliminated from the blood according to one (or several) exponential functions (e.g., Fig. 26). The rate of degradation is only slightly or not at all elevated in alcoholics when compared to nondrinkers and the 25% increase in the rate of excretion is of no importance. Alcohol is initially oxidized

to acetaldehyde in a reaction catalyzed by alcohol dehydrogenase. This is followed by further oxidation to acetic acid and finally carbon dioxide and water. The liver plays an important role in these processes since the first step in alcohol oxidation occurs in that tissue.

In the central nervous system the effect of alcohol is basically no different than that of other anesthetic agents such as ether. Thus all the stages of anesthesia can be produced just as with ether. Practically speaking, such anesthesia cannot be carried out because of the difficulty of controlling the anesthetic level and the narrow therapeutic index. Small or moderate doses of alcohol produce in many individuals, particularly in a suitable environment, an animation of motor and psychic functions. Consequently, in spite of a deterioration in the ability to concentrate and in motor coordination, self-criticism is diminished and the individual appears to be very self-assured. Reaction times are prolonged, particularly in unexpected situations. This combination of psychic changes is particularly dangerous in street traffic. The clinically meaningful alcohol effect can be established in about 50% of those persons having a blood alcohol concentration of 0.1%; with values of 0.05% it is detectable in 20–30% and with 0.2–0.25% in practically all cases including in part severe intoxication. At these high values the anesthetic effects are generally expressed while blood levels of 0.35–0.5% have been found in cases of lethal intoxication. Tests with automobile drivers have shown a demonstrable impairment of their performance with blood alcohol levels of 0.08%. The effects of alcohol are considerably enhanced by the simultaneous administration of psychopharmacological agents, hypnotics, and some antihistamines.

The circulatory effects of alcohol are dependent upon the action of the drug in the central nervous system (cf. p. 42), which results in dilation of the cutaneous vessels. Consequently there is an increase in the loss of heat. Thus intoxicated individuals can die of exposure as the result of the hypothermia. The dilation of the cutaneous vessels does not result in a fall in blood pressure because simultaneously the vessels of the splanchnic bed are constricted. Cardiac output and blood pressure can increase somewhat. A centrally determined (neurogenic) shock can occur with severe alcohol intoxication. Although sometimes subjective complaints in cases of coronary insufficiency are improved by alcohol, no objective EKG changes can be demonstrated because the coronary vessels are not dilated. Vasopressin secretion from the posterior pituitary is inhibited while the alcohol concentration is increasing in the blood. This results in increased diuresis. Alcohol inhibits gluconeogenesis from amino acids, particularly when liver glycogen is depleted. The resulting hypoglycemia can have serious consequences, especially in diabetics maintained on insulin, but also in children. This is especially true since the causes of the loss of consciousness and the convulsions are frequently not recognized and because the concentration of alcohol in the blood may already have diminished.

Acute poisoning with alcohol is treated sympatomatically as an intoxication from sleeping medication (cf. p. 164); artificial respiration, maintenance of a free airway, observation of water and electrolyte balance and temperature regulation, and prophylactic antibiotics are necessary. Infusions of fructose are useful, particularly in the commonly occurring cases of hypoglycemia.

Tolerance

With regular administration of alcohol there is a decrease in the pharmacological activity. This increased tolerance cannot be explained by a change in absorption, distribution, or elimination. One therefore assumes that the central nervous system becomes less sensitive or that the alcoholic learns to produce and accomplish at a higher level than would be possible in a nonalcoholic despite the high alcohol content in his blood. Sometimes a smaller rise in the blood alcohol level has been observed in alcoholics than in normal individuals following the same dose of alcohol. The lethal dose of alcohol is not higher in alcoholics than it is for normal individuals. This also indicates that a more rapid degradation of alcohol in such cases does not occur.

Dependence (for definitions, see p. 336) occurs frequently with alcohol. In some of these cases after a slow or often sudden increase in the daily dose, addiction develops. In relation to the frequency of dependence and its social consequences, alcohol is by far the most important of all intoxicating compounds.

Chronic Alcoholism

Chronic administration of alcohol leads to a series of other organic and mental disturbances in addition to the psychic manifestations of the drug dependency. Besides fatty liver and chronic gastritis (which is often associated with morning vomiting) already mentioned, liver cirrhosis, disturbances of the exocrine pancreas function and erythropoiesis, reduction of the magnesium level in blood, and more seldom chronic renal and heart disease or myopathies can occur. The probability of producing cirrhosis of the liver is dependent upon the daily amount of alcohol consumed (not the type of beverage) and the duration of chronic abuse. Months after the apparent cure of a case of hepatitis, a moderate amount of alcohol is capable of eliciting a relapse. Polyneuritis induced by alcohol appears to be the result of vitamin B_1 deficiency and can be improved by the administration of thiamine. The metabolism of the alcoholic is as dependent upon this vitamin as it is with a pure carbohydrate diet which produces beriberi. One gram of alcohol yields 7.1 calories and therefore replaces carbohydrates to a large extent. Maximally, 70% of the basal metabolic requirements can be met by the continuous administration of ethanol (0.7 calories per kilogram per hour).

Since alcohol must be oxidized, the simultaneous administration of sufficient amounts of carbohydrates or fat can lead to an increased deposition of these nutrients in the tissues. From the standpoint of the physician, it is not desirable that such long-term alcohol administration should form the basis for nutrition because chronic damage must be expected.

The disturbances in cerebral function can be considerable. Wernicke-Korsakow syndrome, acute alcoholic hallucinations, or delirium tremens can occur. Prior to or during such delirium tremens, epileptiform convulsions often take place. They can be elicited by the sudden withdrawal of alcohol from an alcoholic. Renewed alcohol administration following the onset of such psychoses is not capable

of changing their course. Delirium tremens is not characteristic only of alcohol abuse since it also can occur with barbiturate addiction.

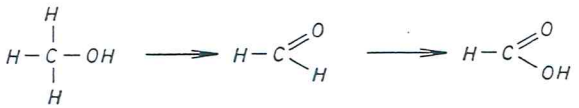
Therapy of Alcoholism

A cure for alcohol addiction is very difficult to attain. Relapses frequently occur following withdrawal from alcohol, particularly since the customs of our society encourage and favor the intake of alcoholic beverages. A long-lasting result can be seldom expected in the absence of effective psychotherapeutic treatment. Complete abstinence is necessary.

Disulfiram (bis[diethylthiocarbamoyl] disulfide). If alcohol is ingested several hours after the oral administration of 1–2 gm of disulfiram, nausea, vomiting, flushing of the skin, cardiac palpitations, and headache occur. The threat of this experience was employed for some time as a deterrent in order to ensure abstinence during withdrawal therapy. Because of its marked side effects disulfiram should no longer be employed.

Methanol

Methanol (methyl alcohol, CH_3OH) is much more toxic than ethanol. Even amounts of 30–50 gm, occasionally even less, have produced lethal intoxication. Since it is widely used in industry, methanol is frequently mistaken for ethanol. Alcoholic beverages obtained on the black market sometimes contain methanol. This alcohol can hardly be considered to produce an "intoxicating" condition. The symptoms of toxicity are not the result of methanol itself, but rather of the formaldehyde produced by its metabolism which is then further oxidized to formic acid.



Methanol *Formaldehyde* *Formic acid*

This degradation occurs more slowly than does that of ethanol, so that the maximum formic acid concentration in the blood is reached only 2 days after administration. The toxic symptoms also develop slowly after a latent period of 18–24 hr. The most important symptoms are partial or total (possibly irreparable) damage to the peripheral visual apparatus, severe acidosis, marked abdominal pain, loss of consciousness or anesthesia, and sometimes oliguria. The changes in vision are related to the action of formaldehyde as are probably the acidosis and the hypoxia. The severity of the acidosis cannot be explained solely on the basis of the formic acid concentration.

Therapy of methanol intoxication involves hemodialysis and treatment of the acidosis by administration of sodium bicarbonate or sodium phosphate (Na_2HPO_4) in amounts which produce a prolonged alkaline reaction in the urine. Such therapy must be continued for 5 days or longer, day and night. In addition, the enzymic degradation of methanol by alcohol dehydrogenase can be inhibited by administering ethanol in quantities which maintain the ethanol blood concentration at 0.1% (substrate competition).

Animal Poisons

Snake poisons have varying compositions, depending upon the species. They contain, along with considerable amounts of enzymes, varying amounts of polypeptides. The enzymes include esterases, proteases, oxidases, and hyaluronidase. A phospholipase A is capable of forming the hemolytic compound, lysolecithin, from lecithin. An enzyme similar to trypsin activates, as does thrombokinase, prothrombin to thrombin. Another constituent of snake poison, "coagulin," converts fibrinogen to fibrin (see also arvin, p. 87). The trypsinlike activity is also shown when incubated together with plasma globulin. This results in the formation of the polypeptide, bradykinin, which stimulates the intestine and acts to decrease blood pressure.

The clinical picture is the result of the increased tendency toward coagulation as well as the necrotizing, hemolytic, and neurotoxic effects. Since histamine is also liberated besides bradykinin, a marked fall in blood pressure is to be expected. The respiratory musculature can be paralyzed by a curarelike action of the poison which is not abolished by neostigmine.

Practically the only poisonous viper occurring in Germany is *Vipera berus*. Its bite is seldom lethal if it occurs on the extremities and not in a vein. Locally, edema, lymphangitis, petechia, hematoma, blisters, and possibly a deep penetrating necrosis occur. Upon absorption there develop within minutes or hours, numbness, headache, dizziness, cardiac palpitations, nausea, vomiting, colic, and circulatory collapse. Hemorrhage in various areas can occur.

There are various poisonous snakes occurring in temperate North America: rattlesnakes (*Crotalus* species), the copperhead (*Agkistrodon contortrix*), water moccasin (*Agkistrodon piscivorus*), and the coral snake (*Micrurus fulvius* and *Micruroides euryxanthus*). The venom of the coral snake contains neurotoxins that induce drowsiness, difficulties in breathing or swallowing, a slow, weak pulse, drooping eyelids, muscular debility, stiffness of the jaw, nausea, vomiting, coma, and eventually death by respiratory and cardiac failure. The venoms of the other species mentioned above are cytolytic with the symptoms of local swelling and pain, necrosis, discoloration of the skin around the bite, and hemorrhage. The necrosis spreads radially from the site of injection, and bleeding from the mucous membranes in the mouth, eyes, nose, and gastrointestinal tract is observed. Hematuria occurs regularly. Death is caused by circulatory failure and preceded by nausea and vomiting.

Therapy of Snake Bites

The use of a tourniquet, the application of ice packs, and incision and suction are recommended to confine and to remove locally active venoms, especially for bites by tropical snakes. For European snake bites, an ice pack is generally suf-

ficient. As soon as possible within the first 2 hr, 10–30 ml of antiserum should be administered intramuscularly.

The poisons of wasps, hornets, and scorpions contain, among other things, large amounts of serotonin. This compound produces pain but is not alone responsible. Wasp poison contains histamine and a bradykinin-like material; hornet poison contains large amounts of acetylcholine as well as a kinin; mosquito venom also contains histamine (the burning nettle also has serotonin, acetylcholine, and histamine); bee venom contains the basic peptides melittin and apamine.

Tetrodotoxin, which is of great experimental interest, can be isolated from East Asiatic fish of the tetraodon species. This poisonous compound specifically inhibits sodium influx during a propagated stimulus in nerves and muscle tissue. Saxitoxin, which acts similarly, has provoked paralysis in man and seabirds after the ingestion of various mollusk species from the Pacific Ocean or the North Sea. The poison, which cannot be destroyed by heat, is produced by dinoflagellates living in the mollusk.

Scorpions are found frequently in the arid southwestern region of the United States. Bites are fairly common and mortality appears to be greatest in children less than 6 years of age. Symptoms consist of mild tingling at the site of sting, which spreads rapidly and is followed by spasms of the throat, restlessness, muscular fibrillation, abdominal cramps, convulsions, and respiratory failure. Unless lethal, the symptoms may last for 24–48 hr. Specific scorpion antivenin is available.

The black widow spider (*Latrodectus mactans*) is a poisonous spider found throughout the United States and Canada and appears to be the only spider in the region dangerous to man. The toxicity of the venom is probably greater than that of snake venom but only a tiny amount is injected with a bite. The area of the bite becomes extremely painful within a half-hour, and the pain then extends to the abdomen, accompanied by evidence of severe shock and muscular spasms. Recovery begins after 12–24 hr and is usually complete within a week. An antitoxic serum has been prepared.

Plant Poisons

Poison Ivy

Poison ivy or poison oak (*Rhus toxicodendron* and *R. diversiloba*) and poison sumac (*R. venenata*) are all related plants that grow widely in the United States. Poisoning may occur from contact with the plants and ingestion or even inhalation of smoke from the burning leaves. Symptoms are a severe dermatitis, consisting of itching, swelling, papulation, and possibly vesiculations and crusting. Severity of the symptoms increases with repeated exposure, indicating that the plant constituents are allergenic. Four compounds have been found in poison ivy, all with the basic structure of urushiol (3-pentadecylcatechol), but with different degrees of unsaturation in the side chain.

The treatment consists mainly of removing the source by washing with soap and applying a bland lotion. It may be important to relieve the severe itching. Desensitization of hypersensitive individuals with commercially available antigens can be attempted. In severe generalized reactions the systemic administration of hydrocortisone or prednisone may relieve the symptoms, but will not shorten the course of the dermatitis, from which recovery is usually complete within 2 or 3 weeks.

Mushrooms

The most frequent poisoning from mushrooms occurs after ingestion of *Amanita phalloides*, the Destroying Angel, since it is mistaken for the common mushroom, genus *Psalloita*. The poisonous compounds are cyclic peptides (molecular weight of approximately 1000) which contain only a few, but in part unusual, amino acids. These peptides are resistant to enzymic degradation in the gastrointestinal tract. They have differing mechanisms of action. Phallotoxin damages the endoplasmic reticulum of the liver cells; amatoxin affects the function of the cell nucleus in the liver, and other organs. The mushroom also contains in small amounts a decapeptide, antamandine, the prophylactic administration of which can hinder to a certain extent the intoxication with amatoxin. After a latent period of 10–20 hr, diarrhea and severe colic occur. Degenerative changes in the heart muscle cells can produce acute cardiac failure. In the following days icterus or acute yellow liver atrophy may result and possibly acute renal failure. Central symptoms such as convulsions, paralysis, and respiratory paralysis can occur. Prompt hemodialysis appears to possibly favorably influence the course of the intoxication; however, the poison is very rapidly bound to plasma protein and cells. In addition, attempts should be made with the usual methods such as glucose or fructose infusions, glucocorticoids, and choline to mitigate the toxic liver damage. Poisoning by *Helvella esculenta* is very similar. The symptoms after the ingestion of *Boletus satanas*, *Lactarius torminosus*, and *Russula emetica* correspond to those mentioned above, although the liver is not damaged to the same extent as following the ingestion of *Amanita phalloides*.

Fly agaric (*Amanita muscaria*) produces symptoms of cholinergic stimulation such as nausea, vomiting, and sweating because of its muscarine content. The principal symptom, however, is a state similar to drunkenness which is not due to muscarine but rather a 3-hydroxyisoxazol derivative with psychotropic activity. Since this symptom is atropinelike, atropine is not suitable as an antidote. Therapy is restricted to central sedation. Poisoning with *Inocyte lateraria* is also the result of the high content of muscarine.

Radioactive Isotopes

If radioactive isotopes are taken up into the body or the body is exposed to the radiation emanating from such isotopes, the same damaging effects must be ex-

pected as occur with X-irradiation. Since biochemically, various isotopes behave differently, the possibilities exist for affecting particular organs with the radioisotope in a differential manner. In this sense, ^{131}I is utilized for irradiation of the thyroid gland. Qualitatively, the mechanism of action of radioactive isotopes is the same. The radiolysis of water leads to formation of H_2O_2 and H_2 as well as highly reactive and therefore cell-damaging products ($H^{\cdot}$, $HO^{\cdot}$ $HO_2^{\cdot}$, O_2^{--}, and H_2^{++}). The danger of a radioactive isotope is not solely dependent upon the quantity of radiation, which is physically measurable, but also upon the character of the radiation. While hard radiation, in contrast to soft radiation, can penetrate more deeply into the body from the outside, the incorporation of the isotope into the body renders soft radiation biologically more effective. After the uptake of radioactive compounds into the body, besides the physical half-life, the biological half-life, which is a measure of the time the isotope remains in the body, is of decisive importance for its potential danger. Those cells with the highest rate of division are the most sensitive, particularly the reproductive cells, the hematopoietic system and the hair-forming epithelial cells. Several hours following a lethal dose of radiation or a radioisotope, nausea, vomiting, and a general feeling of weakness occur. Within 24 hr the number of lymphocytes is reduced, followed by decreases in the leukocyte and thrombocyte counts with a minimum being reached within 7–10 days. The corresponding fall in the erythrocyte count occurring after larger doses of radiation first occurs after 6 weeks as the result of the longer lifetime of these cells. The epithelial lining of the crypts of the small intestine is directly damaged, producing disturbances in gastrointestinal function. As the result of the diminished leukocyte and thrombocyte counts and damage to the intima of blood vessels, infections and hemorrhage (for example, bloody diarrhea) occur. Three weeks after irradiation all body hair can fall out, only to begin to grow after some weeks, if the patient survives. The formation of spermatozoa in the testicles or of follicles in the ovaries is inhibited. Mutations within the reproductive cells can occur as the result of the radiation; these may be expressed only after generations. With chronic exposure to small doses of radiation, morphological changes in the chromosomes can be detected even in clinically healthy individuals. The immediate cause of death following large doses of radiation is related to the loss of bone marrow function, hemorrhage, or infection. A dose of 600 r (roentgens) is probably 100% fatal in man and 400 r, 50%; 200–300 r elicit severe damage. Accumulation of the effects occurs with repeated doses. There is no threshold for the genetic damage. Radioisotopes, as other types of radiation, can lead to the formation of tumors, leukemia, etc., even many years later. The genetic damage produced by radiation and cytostatic compounds can be additive. The exposure to radioisotopes as well as to diagnostic X-rays should be restricted to an absolute minimum during pregnancy since the embryo is particularly sensitive to radiation and the probability for the production of leukemia or malignant tumors is elevated in the child.

Therapy of radiation damage is restricted to symptomatic measures, for example, blood transfusions, antibiotics, etc. The weak protective effects of thiols (cysteine, cysteamine, etc.) is of little importance. Moreover, these compounds are only effective if they are given prior to irradiation.

Carcinogens

The great importance accorded to carcinogens does not need to be emphasized. In the space available for the short presentation of the practical toxicological problems, chemical carcinogenesis can be only superficially surveyed.

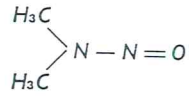
The term "carcinogen" includes all compounds which can induce the degeneration of normal cells to neoplastic cells. Frequently, the final carcinogenic agent is formed in the organism from the "precarcinogen" by metabolic conversion. Along with carcinogenic compounds, other factors are known to elicit cancer, such as ionizing radiation and viruses.

Compounds termed cocarcinogens should be distinguished from carcinogenic compounds. Cocarcinogens include all compounds which are only capable of inducing a neoplastic degeneration in combination with another agent, whether given simultaneously or consecutively.

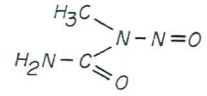
A very large number of carcinogenic and cocarcinogenic compounds are known. They are found among newly obtained synthetic compounds as well as natural products. Research on carcinogenesis is extraordinarily difficult because of the widely varying sensitivity of various organs and species toward carcinogenic materials. The translation of results obtained from animal experimentation to man in this field of experimental medicine is even more difficult than in other areas of research.

Only some of the principal types of carcinogens with representative examples are given below:

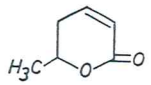
1. Alkylating agents. Some alkylating compounds have already been discussed in the section on cytostatic agents (cf. p. 303) since on the basis of their chemical properties they are capable of chemically changing the nucleic acid in tumor cells so that these cells die. This process can also take place in normal cells. When this occurs, the alkylating compounds act as carcinogens, mutagens, or teratogens.



Dimethylnitrosamine



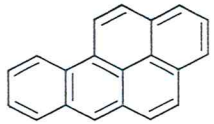
N-Methyl-N-nitrosourea



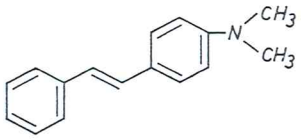
Parasorbic acid, a lactone from the berries of the mountain ash

Along with the cytostatic agents already discussed, lactones and nitrosamine derivatives can also possess carcinogenic activity on the basis of their alkylating properties (examples in the collection of formulas). Since carcinogenic amounts of dimethylnitrosamine can be formed in foodstuffs after the addition of nitrites, there

Polycyclic hydrocarbons and aromatic amines



Benzpyrene



Dimethylaminostilbene

possibly exists a danger for man in the consumption of nitrite-containing meat products.

2. Polycyclic hydrocarbons and aromatic amines. A large number of very potent carcinogens belong to this group. It is assumed that these compounds are attached between two strands of nucleic acid and thereby produce a disturbance in function. Two examples from this group are contained in the collection of formulas.

3. Inorganic compounds. Examples are arsenic, chromium, and asbestos.

4. Radioactive compounds (see p. 369).

Naturally occurring compounds can also be carcinogenic. Examples include the pyrrolizidine alkaloids from the species *Senecio*, tannins, safrole (4-allyl-1, 2-methylenedioxybenzene), parasorbic acid, and components obtained from molds such as aflatoxin from *Aspergillus flavus*.

Teratogens

Most of the carcinogens mentioned above as well as the cytostatic agents (e.g., antimetabolites) can injure the embryo during development. The fetus dies or is born malformed. It should also be remembered that possibly even a single exposure to such agents during embryonic life may be expressed only in the later life of an individual.

CHAPTER **12**

HISTORICAL DEVELOPMENT

13th century	Raymondus Lullius discovers so-called sweet vitriol (ether).
16th century	Theophrastus Bombastus von Hohenheim (Paracelsus) rediscovers sweet vitriol.
1630	Report on the use of cinchona bark in malaria.
ca. 1650	L. Rivière introduces calomel as a diuretic.
1747	J. Lind carries out controlled experiments with citrus juices for the control of scurvy in ship's crews.
1772	J. Priestley, minister and chemist, discovers nitrous oxide.
1785	W. Withering describes the effects of digitalis on the diseased heart.
ca. 1800	S. Hahnemann initiates the homeopathic approach to the treatment of diseases.
1800	H. Davy recommends the use of nitrous oxide to alleviate pain during surgery.
1804	F. W. A. Sertürner succeeds in the isolation of pure morphine.
1811	B. Courtois discovers iodine in the ash of marine algae.
1819	F. F. Runge discovers quinine.
1820	J. Pelletier and B. Caventou succeed in the preparation of pure quinine.
1820	I. R. Coindet introduces iodine for the treatment of goiter.
1821	F. Magendie recommends the use of placebos for controlled clinical investigations.
1831	E. Soubeiran, J. Liebig, and S. Guthry discover chloroform independently of each other.
1842	C. W. Long carries out the first surgery with ether anesthesia.
1844	H. Wells painlessly extracts the first tooth during nitrous oxide inhalation.
1846	J. C. Warren performs surgery with ether anesthesia on the recommendation of C. T. Jackson.
1846	W. T. G. Morton treats teeth with the help of ether anesthesia.
1846	R. Liston amputates with the help of ether anesthesia.
1847	J. Y. Simpson introduces chloroform for anesthesia during birth and surgery.
1847	M. J. P. Fluorens notes the anesthetic effect of chloroform in animal experiments.
1847	R. Buchheim founds the first institute for experimental pharmacology in Dorpat.
1851	L. Traube initiates modern digitalis therapy of heart disease on the basis of animal experiments.
1856	Claude Bernard and A. R. Kolliker

discover the action of curare on the motor end plate.

1860 A. Niemann prepares pure cocaine.

1867 J. Lister introduces phenol for the antiseptic treatment of wounds.

1869 B. Naunyn carries out with animals experimental work on quinine.

1869 O. Liebreich introduces chloral hydrate as a sleeping drug.

1873 E. Klebs, B. Naunyn, and O. Schmiedeberg found the first pharmacological journal, *Archiv für experimentelle Pathologie und Pharmakologie.*

1883 L. Knorr discovers phenazone (antipyrine).

1884 E. Baumann discovers sulfonal.

1884 A. Kast introduces sulfonal as a sleeping drug.

1884 G. Koller discovers the local anesthetic effect of cocaine.

1885 L. Pasteur introduces active vaccination for treatment of rabies.

1887 O. Hinsberg synthesizes phenacetin.

1887–88 F. Loeffler, E. Roux, and A. E. I. Yersin discover the diphtheria toxin.

1889–90 J. v. Mering and O. Minkowski observe that removal of the pancreas leads to symptoms in the dog similar to diabetes mellitus.

1889 J. N. Langley and W. L. Dickinson demonstrate that nicotine first stimulates and then paralyzes ganglion cells.

1890 E. Behring and Sh. Kitasato originate serum therapy.

1890 E. Behring discovers the specific diphtheria and tetanus antitoxins.

1890 E. Ritsert prepares ethoform.

1892 E. Kraepelin founds psychopharmacology.

1895 G. Oliver and E. A. Schäfer discover the blood-pressure elevating effect of extracts from the adrenal gland.

1895 E. Baumann discovers thyroid iodine.

1896 Experiments with birds lead to the discovery of avitaminosis as a cause for beriberi by C. Eijkmann.

1896 F. Stolz prepares aminophenazone which is then introduced into medical practice.

1898 F. Hoffmann and E. A. Eichengrün prepare acetylsalicylic acid and introduce it into therapy.

1901 T. B. Aldrich and J. Takamine isolate crystalline adrenaline (epinephrine).

1902–03 Ch. Richet, M. Arthus, and P. Portier discover anaphylaxis.

1903 E. Fischer and J. v. Mehring initiate the introduction of barbital into therapy.

1904 F. Stolz synthesizes epinephrine.

1904 P. Ehrlich and K. Shiga found chemotherapy with numerous investigations.

1905 A. Einhorn synthesizes procaine.

1906 A. Fraenkel introduces the intravenous administration of strophanthin.

1906 H. H. Dale introduces term adrenaline reversal.

1906 H. H. Dale observes the strong effects of extracts from the posterior lobe of the hypophysis on the uterus.

1908 A. Windaus and W. Vogt succeed in the synthesis of histamine.

1907–10 A. Holst and Th. Fröhlich prove with animal experiments that scurvy is an avitaminosis.

1909 W. Blair-Bell uses extracts from the posterior lobe of hypophysis in postnatal bleeding.

1910 P. Ehrlich and S. Hata introduce arsphenamine for the treatment of syphilis.

1911 M. Dohrn prepares cinchophen, whereupon it is introduced into therapy.

1913 P. Ehrlich introduces acriflavine into the therapy of trypanosome infections.

1913 C. Funk introduces the term vitamin.

1914 H. H. Dale recognizes the importance of acetylcholine and distinguishes its muscarinic and nicotinic effects.

1914 K. F. Wenckebach points out the therapeutic effect of quinine in cardiac arrythmias.

1914 C. Funk isolates vitamin B.

1914 E. C. Kendall isolates thyroxine from the thyroid gland.

1915 I. Pohl prepares *N*-allylnorcodeine, which reverses the respiratory depression produced by morphine.

1916 F. C. McLean isolates heparin from the liver and heart.

1916 W. Howell discovers heparin.

1916 H. Hörlein discovers phenobarbital for therapeutic use.

1917 O. Dressel, R. Kothe, and W. Roehl discover the trypanocidal effects of suramin.

1918 W. Frey introduces quinidine into the therapy of cardiac arrythmias.

1920 The German Pharmacological Society is founded.

1920 P. Saxl and R. Heilig introduce merbaphen as the first synthetic mercurial diuretic.

1921 O. Loewi demonstrates chemical transmission of the nerve stimulus to the effector organ.

1921 H. M. Evans and J. A. Long note increased growth and luteinization of ovaries after injection of extracts from the anterior lobe of the hypophysis.

1921 F. G. Banting, C. H. Best, and J. B. Collip succeed in the isolation of insulin.

1924 K. K. Chen and C. F. Schmidt describe the epinephrinelike effects of *Ephedra vulgaris.*

1924 W. Schulemann, F. Schönhöfer, and A. Wingler prepare pamaquine.

1925–26 K. F. Schmidt, F. Hildebrandt, and O. Eichler introduce pentylenetetrazole into therapeutic use.

1926 O. Loewi and E. Navratil discover acetylcholine after vagal stimulation of the heart.

1926 P. Mühlens and co-workers discover the action of pamaquine, the first synthetic agent effective against human malaria.

1926 B. C. Jansen and W. F. Donath isolate aneurin (thiamine).

1926 G. R. Minot and W. P. Murphy introduce liver therapy for pernicious anemia.

1927 A. Windaus and A. F. Hess discover vitamin D by ultraviolet irradiation of ergosterol.

1927 F. Eichholtz induces anesthesia with tribromoethanol.

1927 J. J. Abel and co-workers succeed in crystallizing insulin.

1927 P. E. Smith finds several hormones in the anterior lobe of the pituitary, among these one with stimulating effects on the adrenal cortex.

1928 A. Fleming discovers penicillin.

1928 A. Szent-Györgyi isolates ascorbic acid.

1929–34 A. Butenandt, E. A. Doisy, E. Laqueur, and T. Reichstein isolate numerous steroid hormones.

1929 W. Roehl initiates the introduction of pamaquine into malaria therapy.

1931 G. Sen and K. C. Bose clinically demonstrate the hypotensive and tranquilizing effect of powdered *Rauwolfia* root.

1931 P. Karrer and co-workers elucidate the chemical structure of vitamin A.

1932 F. Mietzsch and H. Mauss synthesize mepacrine.

1932 W. Kikuth, F. Sioli, and F. M. Peter introduce mepacrine into malaria therapy.

1932 F. Mietzsch and I. Klarer prepare sulfonamidochrysoidine as the first sulfonamide.

1933 H. H. Dale proposes the division of the autonomic nervous system into cholinergic and adrenergic nerves.

1933 H. Weese introduces anesthesia with hexobarbital.

1934 A. Butenandt prepares progesterone from a soybean steroid.

1935 G. Domagk introduces sulfonamides into therapy.

1935 U. S. von Euler isolates a very potent compound from human semen which he names prostaglandin.

1935 P. S. Hench and E. C. Kendall isolate cortisone from the adrenal cortex.

1936 E. Jorpes prepares pure heparin after its discovery in 1916 by W. H. Howell.

1937 R. Kuhn and I. O. Morris synthesize vitamin A.

1937 M. Steiger and T. Reichstein synthesize deoxycorticosterone.

1938 H. H. Merritt and T. J. Putnam introduce diphenylhydantoin as an antiepileptic agent.

1939 P. Müller discovers the insecticidal activity of chlorophenothane (DDT).

1939 O. Eisleb and O. Schaumann introduce meperidine as the first fully synthetic narcotic drug.

1941 Through their research, A. Fleming, E. P. Abraham, E. Chain, C. M. Fletcher, and H. W. Florey make the introduction of penicillin into therapy possible.

1941 E. R. Hart prepares *N*-allylnorcodeine and *N*-allylnormorphine (nalorphine), which counteract the respiratory depression produced by morphine.

1941 H. A. Campbell and K. P. Link identify dicoumarol as the agent producing a bleeding tendency in cattle after feeding with spoiled sweet clover hay.

1942 B. W. Halpern develops phenbenzamine as the first antihistamine.

1942 S. A. Waksman coins the term antibiotic.

1943 C. H. Li, G. Sayers and co-workers isolate corticotropin (ACTH).

1943 H. Weese and G. Hecht develop polyvinylpyrrolidone as a plasma substitute.

1943 K. Unna carries out pharmacological investigations with nalorphine.

1944 A. Loubatières describes the lowering of blood sugar levels by sulfonamides.

1944 S. A. Waksman and A. Schatz discover streptomycin.

1945 B. A. Johnson and co-workers discover bacitracin.

1945 C. H. Li, H. M. Evans, and M. E. Simpson isolate growth hormone.

1946 V. duVigneaud synthesizes penicillin.

1946 F. M. Berger discovers the anticonvulsant drug, mephenesin.

1946 D. Bovet and collaborators develop the first muscle relaxant of the curare type.

1946 J. Lehmann introduces *p*-aminosalicylic acid (PAS) into therapy of tuberculosis based on observations by F. Bernheim

1947 J. Ehrlich, A. R. Bartz, P. R. Burkholder, D. Gottlieb, and coworkers discover and isolate chloramphenicol.

1947 A. Hofmann discovers lysergic acid diethylamide, and W. A. Stoll continues the investigation of its psychotomimetic action.

1948 R. P. Ahlquist describes the α- and β-receptors of the adrenergic system.

1948 B. M. Duggar prepares chlortetracycline.

1948 P. S. Hench and E. C. Kendall describe the antirheumatic effect of cortisone.

1948–49 R. B. Barlow, H. R. Ing, W. D. M. Paton, and E. J. Zaimis discover muscle relaxants of the depolarizing type and ganglion-blocking agents.

1948 K. Folkers and co-workers as well as L. Smith and L. F. J. Parker prepare pure vitamin B_{12}.

1949 S. A. Waksman and H. A. Lechevalier discover neomycin.

1949 J. F. J. Cade introduces lithium into the therapy of mania on the basis of observations in animal experiments.

1950 A. C. Finlay discovers oxytetracycline.

1951 H. Laborit and P. Huguenard introduce chlorpromazine to achieve hypothermia during surgery.

1951 R. W. Berliner and co-workers demonstrate the inhibition of carbonic anhydrase activity by acetazolamide in the kidney.

1952 J. M. McGuire and co-workers prepare erythromycin.

1952 I. C. Müller, E. Schittler, and H. J. Bein isolate reserpine and determine its structure.

1952 R. W. Wilkins introduces reserpine for the treatment of hypertension.

1952 J. Delay and P. Deniker describe the effect of chlorpromazine as a psychosedative.

1953 V. du Vigneaud and co-workers determine the structure of oxytocin and vasopressin and synthesize oxytocin.

1953 F. Sanger and co-workers determine the amino acid sequence of insulin.

1953 F. H. Dost introduces the term pharmacokinetics.

1954 E. Weber and N. S. Kline introduce reserpine into the treatment of psychoses.

1954 F. M. Berger and co-workers describe the effects of meprobamate.

1954 F. H. Shaw and co-workers discover bemegride, a compound with analeptic effects.

1954 S. A. Simpson, J. F. Tait, A. Wettstein, T. Reichstein, and coworkers elucidate the structure of aldosterone.

1954 M. Schou and co-workers systematically investigate with double blind techniques the activity of lithium in mania (cf. 1949).

1955 C. H. Li and co-workers and Bell and co-workers elucidate the structure of corticotropin.

1955–56 J. D. Achelis and K. Hardebeck as well as A. Bänder and J. Scholz report the introduction of sulfonylurea derivatives as orally effective, hypoglycemic agents.

1956 G. Pincus and collaborators perform studies leading to hormonal oral contraceptives.

1956 W. Kunz, H. Keller, and H. Mückter introduce thalidomide as sedative and hypnotic; the polyneuritis and especially the teratogenic effects of this compound lead to a worldwide reappraisal of drug side effects and problems arising from the introduction of new medicinal agents.

1957 R. Kuhn discovers the thymoleptic action of imipramine.

1957 C. M. Kagawa and co-workers discover aldosterone antagonists.

1957 H. Laborit and R. Coirault introduce chlorethiazole into clinical use on the basis of its anticonvulsant and hypnotic activities discovered by R. Charonnat, P. Lechat, and J. Chareton.

1957 F. C. Novello and J. M. Sprague introduce chlorothiazide as the first saluretic from the benzothiadiazine group.

1960 E. W. Sutherland and co-workers demonstrate the importance of 3′,5′-AMP as a "second messenger."

1960 R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. I. Daniel describe the hypotensive effect of guanethidine.

1960 J. A. Oates, L. Gillespie, S. Udenfriend, and A. Sjoerdsma report the hypotensive effect of α-methyldopa.

1960–62 O. Hornykiewicz, H. Ehringer and W. Birkmayer demonstrate a dopamine deficiency in the central nervous system in Parkinson's syndrome and describe the effects of L-dopa.

1963 R. W. Rundles and co-workers introduce allopurinol for the treatment of gout.

1963 S. Bergström and co-workers by clarifying the chemical structures of two prostaglandins open up the possibility of the practical use of this group of compounds.

1963–64 G. V. Foster and co-workers as well as P. F. Hirsch and co-workers recognize the thyroid as the source of calcitonin first described by D. H. Copp in 1962.

1964 E. J. Ariëns and co-workers publish a comprehensive treatment of quantitative receptor theory.

1967 G. C. Cotzias and co-workers introduce L-dopa into the therapy of parkinsonism.

1968–70 M. Bygdeman and co-workers, J. M. Beazly and co-workers, S. M. M. Karim and co-workers demonstrate the clinical usefulness of prostaglandin for the induction of labor.

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"Drill's Pharmacology in Medicine." McGraw-Hill, New York, 1971; L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," Macmillan, New York, 1970; J. J. Lewis, "Introduction to Pharmacology" Williams and Wilkins, 1963. A book which is particularly important in placing the quantitative aspects of pharmacology in the forefront is E. J. Ariens, "Molecular Pharmacology," Vols. I and II, Academic Press, New York, 1964. In addition a comprehensive treatment of general pharmacology is A. Goldstein, L. Aronow, and S. M. Kalman, "Principles of Drug Action." Harper, New York, 1968.

The following periodicals which appear annually are useful to keep abreast of the newest developments in the field: *Annual Review of Pharmacology, Annual Review of Physiology, Annual Review of Biochemistry, Antibiotics Annual* and *New Drugs*. The individual review articles appearing in these volumes are not cited in the following.

In the following we have collected references to the literature which are easily obtainable. No original publications of research are listed but rather review articles. In this way the reader can rapidly orient himself within a field and then read in greater depth, if necessary, from the original literature cited in these reviews. In addition, we have restricted ourselves to review articles primarily from the last decade since the older literature is usually cited in these publications.

The bibliography is arranged corresponding to the chapters of this book and is in alphabetical order.

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